MYOCARDIAL INFARCTION

Committee on Anticoagulants of the American Heart Association 1946–1949

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Myocardial Infarction

ITS CLINICAL MANIFESTATIONS AND TREATMENT WITH ANTICOAGULANTS

A Study of 1031 Cases

by

IRVING S. WRIGHT, M.D.
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DOROTHY FAHS BECK, Ph.D.

This is a report of the
COMMITTEE ON ANTICOAGULANTS,
created by The American Heart Association,
and reflects that Committee's findings
in the matter under study.

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Preface

IN the present phase of our civilization coronary occlusion with myocardial infarction is a major cause of death and disability. It is estimated that each year approximately 200,000 persons die from this cause in the United States and that from 600,000 to 800,000 persons suffer attacks. Probably even the higher attack figure does not represent the true incidence since postmortem evidence consistently reveals many clinically unrecognized infarctions. Perhaps the greatest personal and social significance of myocardial infarction lies in the large number of persons lost by death during their most productive years—years when their talents are most needed by their families, their professional or industrial groups and their nation. Moreover, while some workers have emphasized only the resultant deaths, a comprehensive view of the cost must include also such serious residual disabilities as myocardial and coronary insufficiency and the results of embolization—hemiplegia, mesenteric occlusion or the loss of a limb from gangrene.

Coronary occlusion with myocardial infarction presents a formidable challenge to the medical profession, but one which was for the most part met passively until the last decade. Prior to this time, etiological factors were the subject of speculation rather than intensive analysis, and treatment was expectant rather than dynamic. Therapy had not progressed much beyond that used during previous centuries, consisting almost exclusively of rest and sedation.

During the past fifteen years certain factors have produced a change in the thinking of numerous students of this subject. The first of these was the more complete realization of the major role played by thrombosis and embolization in the production both of the original infarction and of its subsequent effects in terms of death and disability. A second was the development of new tools in the form of anticoagulants which are capable of preventing or retarding the formation of thrombi and encouraging their dissolution. Third, and perhaps of greatest ultimate significance, has been the increase in knowledge regarding the pathogenesis and possible prevention of atherosclerosis. This report concerns itself primarily with the first two of these factors.

Following original reports which suggested that the use of anticoagulants might influence favorably the outcome of an attack of coronary thrombosis with myocardial infarction, the American Heart Association, in 1946, established a Committee on Anticoagulants with the mission of evaluating this form of therapy. The details regarding the origin, purpose and plan of this study are presented in Chapter II. A preliminary report of the results of this study based on 800 patients divided into treated and untreated groups was published in 1948.[282, 283] The major hypothesis was found to be valid; namely, that anticoagulant therapy could influence favorably the prognosis in myocardial infarction. In the course of this study a very large mass of data relating not only to anticoagulants and their use but also regarding myocardial infarction both as a pathological process and as a clinical syndrome has been accumulated. During the past seven years these data have been subjected to intensive analysis by a team of statistical personnel working under Dr. Beck and with physician members of the Committee.

Emphasis has been on a search for facts, very careful consideration being given to all factors which might produce bias. Because of lack of space the preliminary reports could

not include all of the details upon which the figures were based. Criticism, based apparently on the lack of understanding of this fact, has appeared from time to time. Because of this and other pressures, there has been a temptation to hasten the publication of the final report. This has been resisted in order that a larger proportion of the valuable material available might be included here.

From the beginning, full cognizance has been taken of the difficulties involved in a study of this magnitude and complexity. The cooperation necessary on the part of about 100 persons operating in 16 widely separated hospitals was exacting, and the response, on the whole, exceptional. That this could be accomplished is a tribute to the teams in these hospitals who were willing to relinquish their individual routines and accept other criteria and techniques of operation in order that the answer to this problem might be obtained at the earliest possible date. Because of this cooperative effort, it was possible to give a preliminary answer in two years instead of the eight or ten that would probably have been required if numerous small clinical trials had proceeded independently. Additional experience and analysis both by the Committee and by more than twenty teams of independent workers in this country and abroad who have analyzed series in which cases treated with anticoagulants were compared with cases not treated with anticoagulants have confirmed the original conclusions in all major tenets. There are a very large number of conclusions in this volume. It cannot be expected that every reader will agree with all of them. These conclusions were drawn after an objective and searching analysis of the data accumulated in this study because they appeared to the authors to be justified by the evidence. They have been concurred in by the Committee.

It was the purpose of this study to determine what could be accomplished by anticoagulant therapy under reasonably favorable conditions. Although the responsible investigators in the 16 cooperating hospitals were selected because of their eminence and qualifications as specialists in cardiology, it should be pointed out that, prior to the beginning of this study, many of them had had limited experience, or no experience, with anticoagulant therapy. The results of this study therefore demonstrate what can be accomplished under circumstances of this kind. Some other workers, reporting what may take place when poorly trained physicians, inexperienced in this technique, use it without adequate instruction, have claimed minimal benefits from anticoagulant therapy. Even under conditions less favorable than those in the present study, however, improvement in the results of anticoagulant therapy can be achieved provided the physicians concerned secure adequate instructions and follow them carefully. Therefore, for the convenience of physicians wishing to apply anticoagulant therapy, we have included as Appendix D, page 500, of this report instructions for administering the various types of anticoagulants now in use.

While this report is presented in great detail and all important tables are included, it is realized that all chapters will not be of equal interest to every reader. For example, clinicians will doubtless find Chapters II through IV, dealing with the origin, purpose and plan of the study and the composition of the sample, of less interest than later chapters which compare the control and treated groups with respect to the clinical course, the techniques and results of treatment, and the autopsy findings. On the other hand, those with statistical interests, or those who may wish to organize a similar study for other drugs may find Chapters II through IV interesting, and it is hoped, helpful. To facilitate a quick grasp of essentials, summaries are included at the end of each chapter. Detailed tables presenting the basic data are included in Appendix F for the

free access of all who are interested. It is hoped that further study of these tables by others will uncover additional findings of interest or importance.

Acknowledgment to all who have contributed would be a pleasant, but an almost impossible task. First, appreciation must go to those responsible investigators (listed in Table 1, Chapter II) who headed the teams in each of the participating hospitals, and to the many members of the staffs of these hospitals who carried the burden of daily observations and the recording of these on master forms. Those indicated by the responsible investigators as having participated to a degree warranting special mention are also listed in Table 1.

We next acknowledge with gratitude the help received from our statistical consultants, Miss Marjorie Bellows and Dr. John W. Fertig The following technical consultants also contributed to the ultimate success of the project: the late Dr. Ralph S. Overman, research chemist in the Central Laboratory, supervised the prothrombin determinations done at The New York Hospital and consulted freely concerning problems arising in relation to the prothrombin determinations throughout the entire study. Dr Charles Brambel of Mercy Hospital, Baltimore, also cooperated closely in a similar manner and spent much time and effort in correlating the prothrombin readings reported by the various participating hospitals.

Coordination, field contacts and supervision from the Central Laboratory were in the early stages the functions of Dr. Ray Vander Meer. He was later succeeded by Dr. Charles D. Marple. Dr. Marple also reviewed all case reports and autopsy protocols forwarded to the Central Laboratory by the participating hospitals and was responsible, in general, for the interpretation of the medical information from these reports. He was assisted in interpreting and classifying the autopsy protocols by Drs. Victor De Wolfe, Research Fellow, and Reese Pritchett, member of the house staff at The New York Hospital.

The execution of the statistical analysis was closely supervised by Dr. Dorothy Fahs Beck, statistician, with the cooperation, advice and recommendations of Dr. Marple and myself. The actual analysis was accomplished by a team of statistical personnel who labored long, carefully and patiently over infinite details. This staff has included Jane Jackson, Bobbetta Gove, Katherine Killeen, Phyllis B. Michelsen, Zenia Odes Fliegel, Florence Perlmutter, Mildred Grossman Williams, David Fox, Mary K. Fontaine and Dare Reid. Mrs. Jane Jackson, in addition, represented the authors in seeing the manuscript through press and verified references. Mr. Paul Newman, medical artist, was responsible for the drawing of the 180 figures included in the report, a project of some magnitude in itself. The index was prepared by Mr. Harry Ellis. Chief among the secretaries who have typed and retyped the manuscript through numerous revisions are Mrs Jean Roeder, Mrs. Virginia Butts, and Mrs. Effie F. Bynum. The proofreading of the manuscript was accomplished with the assistance of Mrs. Janet B. Prince. Grateful acknowledgment is made to each and every member of these teams whose joint efforts have created the report here presented.

Grateful appreciation is herewith also acknowledged for the support of the American Heart Association, its officers and staff and to the National Heart Institute for its grants-in-aid which made this study possible. Acknowledgment is made to the Samuel Kress Fund for support in this project. Gratitude is expressed to the New York Heart Association for the provision of office space for the statistical staff for a three-year period from 1950 to 1953 and to Dr. Wilson G. Smillie and to the Kips Bay-Yorkville District Health Center of the New York

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It was the purpose of this study to determine what could be accomplished by anticoagulant therapy under reasonably favorable conditions. Although the responsible investigators in the 16 cooperating hospitals were selected because of their eminence and qualifications as specialists in cardiology, it should be pointed out that, prior to the beginning of this study, many of them had had limited experience, or no experience, with anticoagulant therapy. The results of this study therefore demonstrate what can be accomplished under circumstances of this kind. Some other workers, reporting what may take place when poorly trained physicians, inexperienced in this technique, use it without adequate instruction, have claimed minimal benefits from anticoagulant therapy. Even under conditions less favorable than those in the present study, however, improvement in the results of anticoagulant therapy can be achieved provided the physicians concerned secure adequate instructions and follow them carefully. Therefore, for the convenience of physicians wishing to apply anticoagulant therapy, we have included as Appendix D, page 500, of this report instructions for administering the various types of anticoagulants now in use.

While this report is presented in great detail and all important tables are included, it is realized that all chapters will not be of equal interest to every reader. For example, clinicians will doubtless find Chapters II through IV, dealing with the origin, purpose and plan of the study and the composition of the sample, of less interest than later chapters which compare the control and treated groups with respect to the clinical course, the techniques and results of treatment, and the autopsy findings. On the other hand, those with statistical interests, or those who may wish to organize a similar study for other drugs may find Chapters II through IV interesting, and it is hoped, helpful. To facilitate a quick grasp of essentials, summaries are included at the end of each chapter. Detailed tables presenting the basic data are included in Appendix F for the

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City Department of Health for office space for the statistical staff during its early period of operation.

Finally, appreciation is expressed to the Albert and Mary Lasker Foundation for a grant toward the publication of this report, which has made it possible to present it to the medical profession at a greatly reduced cost, and to our publishers for their splendid cooperation in the production of this volume in suitable form.

IRVING S. WRIGHT, M. D., Chairman
Committee on Anticoagulants of the American Heart Association

Contents

CHAPTER 1

Introduction: The Background of This Study

THE possibility of using anticoagulants clinically for the prevention and treatment of coronary thrombosis with myocardial infarction was suggested by Solandt, Best and co-workers following a series of ingenious animal experiments reported in the years 1936 through 1940.[20] Best and his associates had produced intravascular clots by a variety of both mechanical and chemical means and demonstrated that these artificially produced intravascular clots could be prevented or at least inhibited by the use of the anticoagulant, heparin, started before, and continued until after the experiment.[21, 157, 158]

In 1938, Solandt and Best[222] produced coronary thrombosis consistently in experimental animals by injecting a solution of sodium ricinoleate into an isolated coronary artery. A thrombus formed in almost every instance when no heparin was used. When, however, the animals were heparinized prior to the injection of ricinoleate, thrombus formation was an exceedingly rare occurrence.

Solandt, Nassim and Best[223] also produced large mural thrombi in the left ventricle of dogs by ligating the anterior descending branch of the left coronary artery and then injecting sodium ricinoleate into the myocardium just beneath the endocardium. Large mural thrombi formed promptly and consistently when the animals were not heparinized, but no mural thrombi were laid down when the administration of heparin was started well before the experiment.

Although reports dealing exclusively with the clinical use of anticoagulants in the treatment of coronary thrombosis and myocardial infarction did not appear in the American scientific literature until December 1945, as early as 1941 some physicians had administered heparin or dicumarol, particularly the latter, to individuals or to small numbers of patients with coronary occlusion. In addition, an increasing experience with the use of anticoagulants in the treatment of venous thrombosis and in the prevention of embolization postoperatively and postpartum had been rewarded with encouraging results.

Levine, Erlinger and Smith* used heparin to treat 4 cases of acute coronary thrombosis at the Peter Bent Brigham Hospital between July 1941 and May 1942, but were forced to terminate the study because of the pressure of wartime conditions. Barker at the Mayo Clinic and Wright and Duryee in New York used dicumarol with apparent success in small numbers of cases of coronary thrombosis prior to 1945, but these cases were not reported at the time.

In papers reporting the use of dicumarol in the treatment of thromboembolic conditions generally, there was occasional reference to the use of dicumarol in acute coronary thrombosis. Lam[110] reported the use of dicumarol in 3 cases of coronary thrombosis with recovery and Evans,[57] in one case with recovery. Gefter, Kramer and Rheinhold[71] reported the use of dicumarol in one case of coronary thrombosis with fatal outcome. Townshend and Honigman[231] reported 3 cases of acute coronary thrombosis among 40 cases of various thromboembolic condi-

* Levine, S.: Personal communication.

tions in which dicumarol was used. LeFevre[113] discussed 7 cases of coronary thrombosis among the 98 cases of all types of thromboembolic conditions in which dicumarol therapy was used. All seven patients recovered.

Holten and Lundsteen[91] reported in 1942 that they had treated 21 patients suffering from coronary thrombosis with heparin, administered intravenously in a dosage of 1.5 mg./kg. of body weight four times a day for periods of from two to four days only. Of the 21 patients so treated, 7 died, 2 within 24 hours following admission to the hospital. Not one of these 21 patients exhibited symptoms or signs of thromboembolism. Of 20 patients with coronary thrombosis treated similarly but not given heparin, 12 died. In a group of 71 recently observed coronary patients not treated with heparin, thromboembolic processes had been discovered during life or at autopsy in 12 instances, or in approximately 17 per cent of the group.

In 1946, Holten[90] summarized his experience in treating coronary thrombosis with anticoagulants. He had first used heparin alone but later utilized combined therapy, starting patients on heparin and dicumarol and continuing their treatment with dicumarol alone. He had observed 170 patients with myocardial infarction between 1940 and 1945. Eighty patients had been treated with anticoagulants and 22 of these had died. Ninety patients had not been given anticoagulants and 52 of these had died. Fourteen patients died within 24 hours and were not considered further in the analysis or in the percentages quoted.

Of patients under 60 years of age not receiving anticoagulants, 27 per cent died; of those receiving anticoagulants, 20 per cent died. In patients over 60 years of age not receiving anticoagulants, 62 per cent died; of those treated with anticoagulants, 37 per cent died. In the total series, 49 per cent of patients not receiving anticoagulants and 25 per cent of patients receiving anticoagulants died.

Peripheral arterial thromboembolic complications were demonstrated at autopsy as follows: Among 77 patients who did not receive anticoagulants there were 41 autopsies, and 15 peripheral thromboembolic complications were discovered. Among the 80 patients who were treated with anticoagulants, there were 26 autopsies, and only 4 peripheral thromboembolic complications were discovered. The author concluded that the purpose of treatment with anticoagulants seems to be the prevention of peripheral thromboembolic complications originating from mural thrombi.

The first American report concerned exclusively with the use of dicumarol in the treatment of a sizable group of patients with coronary thrombosis and myocardial infarction was that by Wright in December 1945.[250] Beginning in 1942, Wright had observed a series of patients which finally reached a total of 76 to whom dicumarol had been administered during the period immediately following coronary thrombosis. Forty-three of these patients had been selected for dicumarol therapy because they had suffered repeated attacks of coronary thrombosis, or repeated thromboembolic phenomena elsewhere in the body, or both types of episodes within short periods of time. Thirty-three patients suffering from a first or second recognized attack of uncomplicated coronary thrombosis were also included in the series.

Fifteen of these 76 patients died, and 61 patients recovered from the attack studied. Whereas 43 patients had been selected because of an extremely grave prognosis, only 11 of these died as a result of the attack for which they were treated. Thirty-eight exhibited no evidence of propagation of the original thrombus or of other thromboembolic phenomena once dicumarol therapy had been instituted. Of the 33 patients having an uncomplicated first or second attack, only 4 died. Postmortem examinations showed that mural thrombi tended not

to extend, but to become smooth and sealed over when dicumarol therapy was instituted.

Wright[234] reported his experience with these cases in more detail before the California Heart Association in October 1945. He concluded that:

1. In no instance was there any evidence that dicumarol aggravated or complicated the course of any of these patients with coronary thrombosis.

2. No serious hemorrhagic complications had been encountered.

3. Anticoagulant therapy appears to be physiologically sound where there is a *tendency* for a thrombus to propagate or for multiple thromboembolic phenomena to appear. Such tendencies appear to have been interrupted and the mortality rate reduced by the use of dicumarol though the series was too small to draw final conclusions.

4. There was no evidence clinically or pathologically in this small series that intimal hemorrhage is an important factor in the etiology of coronary thrombosis with myocardial infarction.

In his original papers and in subsequent publications, Wright[231, 232, 234, 235] emphasized repeatedly the following observations and conclusions:

1. Dicumarol may be of value as a preventive measure against the propagation of coronary thrombi, against multiple attacks of coronary thrombosis within short periods of time, against mural and thebesian vein thrombosis, and against thromboembolic phenomena following coronary thrombosis. Dicumarol may be of use in the treatment of such complications when they arise in association with auricular fibrillation

2. Although the use of dicumarol might be indicated as a routine measure in all cases of coronary thrombosis, the accumulated experience did not justify the recommendation that dicumarol be used in uncomplicated cases of coronary thrombosis.

3. There was no evidence that once dicumarol had been discontinued and the plasma prothrombin time returned to normal there is any less risk to the patient that he will suffer a subsequent attack of coronary thrombosis.

4. A detailed and statistically valid study of a large group of patients is necessary to establish the value of dicumarol in the routine treatment of coronary thrombosis. "Adequate controls with which to determine the value [of dicumarol] statistically are not yet available and will be of little value unless several subdivisions depending on the severity, extension and complications of each group are studied separately. Each of these subdivisions must contain a statistically significant number of controls and treated patients. This will be a long and difficult but important evaluation."

In January 1946, Nichol and Page[144] reported that they had administered dicumarol to 44 unselected private patients in 50 attacks of acute coronary thrombosis during a period of two and one-half years. The immediate mortality rate was 16 per cent All 26 of the patients who were treated in their first attack survived. No mural thrombi or systemic or pulmonary embolic phenomena were found in the 6 cases examined postmortem. In one instance there was clinical evidence of pulmonary embolism but the patient had received an ineffective dose of dicumarol. These authors concluded that dicumarol is a reasonably safe drug if used intelligently and that it probably decreases the immediate mortality rate in acute coronary thrombosis. They felt that it nearly always prevents pulmonary and systemic thromboembolism if used in adequate amounts.

Peters, Guyther and Brambel[138] reported in February 1946 that they had studied 110 cases of coronary thrombosis with myocardial infarction. Sixty patients had received

the accepted conservative treatment for coronary thrombosis. Fifty patients had received identical treatment except for additional therapy with dicumarol in amounts sufficient to maintain a plasma prothrombin activity of from 35 to 50 per cent of normal. In the group of patients not receiving dicumarol the incidence of clinical embolism was 16 per cent and the mortality rate, 20 per cent. In the group of patients who were treated with dicumarol, the incidence of clinical embolism was only 2 per cent and the mortality rate only 4 per cent.

The authors comment that they had observed an increased clotting tendency in most of their cases of acute coronary thrombosis as manifested by a shortening of the prothrombin clotting time of 12.5 per cent diluted plasma. Dicumarol could be administered safely to patients with coronary thrombosis to interfere with this tendency to accelerated clotting. They felt that the incidence of embolism as a complication of coronary thrombosis was reduced significantly in this series of cases by maintaining the prothrombin activity of the blood between 35 and 50 per cent of normal for a period of approximately 6 weeks. They had noted few toxic reactions and felt that the drug could be administered indefinitely without ill effect.

They concluded that their dicumarolized patients had experienced only one-eighth as many thromboembolic complications, that only one-fifth as many had died as among those patients not treated with dicumarol, and that such a reduction appeared sufficiently significant to warrant further clinical evaluation of dicumarol.

SUMMARY

At the time the present study was initiated, heparin had been used successfully in preventing or in reducing in size myocardial infarction produced by experimental coronary occlusion in animals. Appropriate techniques for the clinical administration of both heparin and dicumarol had been developed and early clinical trials had shown promising results in both the prevention and treatment of thromboembolism in a wide variety of conditions. Encouraging results from the use of anticoagulants in several small clinical series as well as in isolated cases of myocardial infarction had been reported in the literature. In each series employing control groups, both the immediate mortality and the proportion of cases showing thromboembolic complications were substantially reduced. In no instance, however, had the number of patients included in the control and treated groups in these studies exceeded 100 cases each. The smallness of these samples and the presence of numerous other uncontrolled factors rendered these findings inconclusive and made a large cooperative statistical study seem appropriate.

These studies constitute the background from which the present study was conceived and planned. Since this time, many other series have been reported in the literature. These are not reviewed in the present chapter but their findings in many cases will be referred to briefly for comparative purposes in later sections of the report.

CHAPTER II

Origin, Purpose and Plan of the Study

THE variables which may influence the results of a study of a series of cases of coronary occlusion with myocardial infarction are both numerous and complex. Included among them are such factors as the age and sex of patients, their medical history, particularly in respect to congestive failure, diabetes, hypertension and previous infarctions, the severity of their attack, and the care they receive. The importance of considering such variables has been stressed by various authors[61, 209, 214] and is also obvious from data presented in later chapters of the present report. It is obviously unwarranted to draw conclusions regarding the results of a given therapy unless these variables are considered in the analysis or in the experimental design, or both For such consideration an adequate number of patients must be observed. The recognition of these requirements suggested the need for an extensive and controlled cooperative study of the use of anticoagulants in the treatment of coronary occlusion with myocardial infarction.

FORMATION OF THE COMMITTEE

In the spring of 1946, the Board of Directors of the American Heart Association authorized the formation of a Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction. The Committee, in turn, planned the study in such a manner as to attain a wide experience with the use of anticoagulants in coronary occlusion over a relatively short period of time and to obtain data of sufficient extent and sufficiently well-controlled to permit a detailed statistical analysis.

The goal set by the Committee was one thousand observed cases of coronary occlusion with myocardial infarction. One-half of these cases were to be treated in the participating hospitals by the conservative methods currently in use. These cases would serve as controls. The remaining cases were to be treated similarly except that [illegible]

The study has been carried out under the auspices of the American Heart Association and with the financial support of the United States Public Health Service, the Samuel H. Kress Foundation, the Albert and Mary Lasker Foundation and others.

The senior author, Dr. Irving S. Wright, served as Chairman of the Committee. (The members of this Committee are listed facing the title page.) The study was coordinated from The New York Hospital Vascular Disease Research Laboratory of which he is Director, and all reports were forwarded to [illegible] Laboratory."

PLAN OF THE STUDY

The Participating Hospitals

Sixteen hospitals in the United States cooperated in observing and reporting cases for this study. From each of these hospitals a responsible investigator was appointed to the Committee and this investigator, in turn, developed his own team locally to study individual cases and report them to the Central Laboratory. The participating hospitals, the responsible investigators, and those [illegible]

TABLE 1

PERSONNEL IN THE COOPERATING HOSPITALS: Personnel in the Cooperating Hospitals Who Participated in the Clinical and Laboratory Aspects of the Study*

Hospital	Responsible Investigators	Clinical Assistants	Laboratory Supervisors and Assistants
Bellevue, New York	John E. Dietrick, M.D.	Edward Holcomb, M.D.	Miss Alice Kerrigan
Beth Israel, Boston	*Herrman L. Blumgart, M.D.*	*A. S. Freedberg, M.D.* H. D. Lewis, M.D. Robert Goldstein, M.D.	
Cincinnati General	Johnson McGuire, M.D. Helen I. Glueck, M.D.	Victor Strauss, M.D. John Pearson, M.D.	Miss Jean Noertker
Cleveland City	Roy W. Scott, M.D.	Henry A. Zimmerman, M.D.	Miss Ileen L. Kroh
Henry Ford, Detroit	F. Janney Smith, M.D.	Ralph M. Denham, M.D. O. H. Janton, M D.	Victor Schelling, Ph.D.
Jackson Memorial, Miami	E. Sterling Nichol, M.D.	David W. Fassett, M.D. Robert Z. Edwards, M.D. *J. F. Keeley, M.D.* William C. Phillips, M D William H. Shafer, M D.	
Lakeside, Cleveland	Harold Feil, M.D. Joseph M. Hayman, Jr., M.D.	John W. Martin, Jr , M.D. Donald B. Cameron, M.D.	
Massachusetts General, Boston	Howard B. Sprague, M.D.	Fred Alexander, M D. Lloyd R. Evans, M.D. Robert J Whipple, M.D Addison L. Messer, M D.	Miss Margaret Rourke
Michael Reese, Chicago	Louis N. Katz, M.D.	H K. Hellerstein, M D. M Dolgin, M.D. L Horlick, M.D. M Feldman, Jr., M D.	
Mt. Zion, San Francisco	John J Sampson, M D.	René Bine, Jr , M.D. Isadore M. Singer, M D.	G. R. Biskind, M.D. Paul Aggeler, M D.

TABLE 1 (cont.)

Hospital	Responsible Investigators	Clinical Assistants	Laboratory Supervisors and Assistants
The New York Hospital, New York	Irving S Wright, M.D Harold J. Stewart, M.D.	Ray Vander Meer, M.D. Charles D. Marple, M.D. Abbott A. Newman, M.D. Victor de Wolfe, M.D. C. W. Sorenson, M.D. R. B Failey, Jr, M.D. R. Prichett, M.D.	Ralph S. Overman, Ph.D. Miss Margaret Todd Miss Gladys MacNichol Miss Kathleen Taylor
Pennsylvania, Philadelphia	Joseph B. Vander Veer, M.D	David S. Marshall, M.D. P T. Kuo, M.D.	Miss Ruth Williams, B.A.
Peter Bent Brigham, Boston	Samuel A. Levine, M.D	W. Proctor Harvey, M.D	Clement A. Finch, M.D.
Rhode Island, Providence	Frank B. Cutts, M.D.	Charles L. York, M.D Wilbur H. Manter, M.D John A. Kincrel, M.D. Bernard Rapoport, M.D W J H. Fischer, Jr, M.D.	Russel O. Bowman, Ph.D.
San Francisco, San Francisco	John J Sampson, M.D	Norman Sweet, M.D. Ernest Rogers, M.D.	Paul Aggeler, M.D. Miss Joyce M. Amluxen
Veterans Administration, Bronx, New York	Louis A Kapp, M.D	Arthur C. DeGraff, M.D Irving Graef, M.D Walter Newman, M.D.	

* For personnel participating in other aspects of the study, see the Preface.

widely distributed over the United States, there was no attempt made to obtain an even geographical distribution. The principal criteria in the selection of hospitals were the presence of a well-supervised cardiac service and the willingness of the local staff to undertake what was expected to be a long and painstaking clinical study.

In each of the participating hospitals, the responsible investigator supervised and was responsible for the observation and treatment of each patient included in the study and for the recording and reporting to the Central Laboratory of information on each case observed in this study. He was assisted by personnel selected from the resident staff or by fellows in cardiology or research associates and by the laboratory staff which performed the daily prothrombin times and other essential laboratory studies.

Criteria for the Diagnosis of Coronary Occlusion with Myocardial Infarction

The original instructions to the participating hospitals stated that "all cases which are diagnosed as having coronary occlusion are to be included in the study, but no doubtful cases are to be included. Each member of the

Committee (the responsible investigator in a particular hospital) is expected to certify as to the diagnosis of each case." However, the following criteria were suggested as guides to the diagnosis:

"a. Typical, progressively changing electrocardiographic records.
b. *Pain, typical in quality and location.*
c. Development of a pericardial friction rub.
d. A drop of 30 mm. or more in the systolic and diastolic blood pressures during the first 48–72 hours.
e. Development of shock, with ashen gray color, cold clammy skin, apprehension.
f. Tachycardia over 90/min. during the first 48 hours.
g. Leukocytosis of 10,000 or more during the first 48 hours.
h. Acceleration of the sedimentation rate to above normal by the third or fourth day.
i. Fever of a degree or more Fahrenheit by the end of 48 hours."

It was the feeling of the Committee that the diagnosis of coronary occlusion with myocardial infarction should rest primarily *in the hands of the responsible investigator* observing the case. The responsible investigators were selected with this requirement in mind.

The report of each individual case forwarded to the Central Laboratory by the responsible investigators included in detail the information upon which the diagnosis had been based, including a resume of the symptoms presented by the patient, the initial physical findings, the evolution of the electrocardiographic pattern, and the initial and subsequent laboratory observations. These reports were reviewed carefully and in every instance where there was any question as to the diagnosis, or where the information provided on the reporting form was insufficient to prove the diagnosis, the report was returned to the responsible investigator with the request that he review it. The actual number of cases dropped from the program as a result of review in the Central Laboratory because of the uncertainty of the diagnosis of coronary occlusion with myocardial infarction was small. Careful study has confirmed the belief that *the diagnoses were well authenticated clinically* in the great majority of cases presented in this report.

It is recognized that the diagnosis of coronary occlusion with myocardial infarction is sometimes difficult to establish. In this study, the opinion of the local investigator, based upon total evidence, both clinical and electrocardiographic, was accepted (though not always without referring the protocol back to him for review) as the most valid basis for including the case in the series.

A review of the case reports indicates that only a very small number of patients failed to exhibit electrocardiographic changes compatible with, if not diagnostic of, myocardial infarction. A more detailed review by Drs. I. S. Wright and V. DeWolfe of the 69 cases collected in The New York Hospital resulted in only *one* case being discarded from the local series because of the uncertainty of the presence of infarction clinically. Finally, examination of the autopsy reports for the 91 *fatal cases on whom postmortem* examinations were performed revealed a myocardial infarction in all but two instances.

The Selection of Cases for Treatment or Nontreatment with Anticoagulants

The instructions for treating or not treating a given case with anticoagulants were as follows: "If a case (patient) is *admitted* on an odd day of the month, anticoagulant therapy will be started. If a case is admitted on an even day of the month, no dicumarol or heparin will be given. Nevertheless, daily prothrombin times are to be done." The alternate-day method of selecting cases for treatment was used instead of an alternate case method to avoid confusion in the management of individual patients and to in-

sure that the sample selected for anticoagulant therapy was truly a random one. This technique will be discussed in the section of this report dealing with statistical methods.

The date of the latest admission to the hospital for any reason was used as the factor in selecting cases for treatment with anticoagulants, not the day on which the occlusion occurred or on which the diagnosis was made. Treatment was instituted on this basis at whatever time the diagnosis of coronary occlusion with myocardial infarction was made, provided the patient had been hospitalized by this time. The day of the onset of the attack was used, however, throughout as the date from which the day of the illness was computed.

A statistical examination of the results of this procedure indicates that some nonrandom influences affected its application. The prescribed selection procedure would be expected to yield, except for chance variations, the same proportion of odd-day (treated) cases as there were odd days of the month during the period of study, namely, 51.0 per cent. If this were the true proportion of odd-day admissions and only chance factors were operating, 19 samples in 20 of this size would be expected to show a percentage of odd-day cases somewhere between 47.9 per cent and 54.1 per cent. Actually 55.3 per cent of all cases were reported to have been admitted on odd days.[a] Such a difference would be expected less than once in 100 times on a chance basis and is statistically significant. One should look, therefore, for factors other than chance that might have operated to produce this excess. While such extraneous factors as weekends, holidays, weather, and administrative arrangements for admission also influence this proportion, such factors would be expected in general to equalize each other in any study covering many months and 16 hospitals. Therefore, the most plausible explanation would appear to be that as physicians observed the benefits of anticoagulant therapy, they speeded up, where feasible, the hospitalization of those patients with coronary attacks who would routinely have been hospitalized on an even day in order to bring as many as possible under the odd-day deadline. This hypothesis is consistent [illegible] that a higher proportion of treated cases were private cases, had private duty nurses, and were severe at onset[c] since one would suspect that such efforts to speed hospitalization to meet an odd-day deadline would occur particularly frequently in the case of private patients suffering severe attacks. Doubtless other forms of manipulation of assignments to the treated group also occurred [illegible] in statistical counts. Fortunately for the study, the overbalance of odd-day admissions does not appear to have been produced in a manner that was sufficiently selective to destroy the approximate initial comparability of the control and treated groups in most respects, as numerous later comparisons will demonstrate. The slightly greater severity at onset of the treated group would be expected to favor the control group in the experiment. A correction for this difference has been made in the death figures cited on page 306, footnote c.

The procedures for the selection of the

[a] This excess does not include even-day cases for whom exceptions were made in treatment. After the switching of some cases to adjust for some types of exceptions, the percentage of the total sample in the treated group rose to 57.1.

[b] The difference in average days before hospitalization was slight (2.7, control, vs 2.4, treated) and was not statistically significant.

[c] In the control group, 35.3 per cent of the cases received other than ward care; in the treated group, 40.9 per cent. In the control group, 20.2 per cent were severe at onset; in the treated group, 30.7 per cent. These differences are not statistically significant at the significance level adopted for this study but they may, nevertheless, be due to nonchance factors, although this remains unproved

sample prescribed further that patients dying within the first twenty-four hours following their admission to the hospital be excluded from both control and treated groups because of the special difficulties involved in the analysis of such cases. These difficulties include the paucity of information obtainable from many of these patients, the incompleteness and inadequacy of the medical and laboratory studies, and the problem of assigning patients who had been given a single dose of dicumarol to the treatment or nontreatment group for analysis. Obviously, anticoagulant therapy could have had no effect on the outcome of the illness in these patients, yet they would have fallen, if admitted on odd days, into the "treated group." These patients were the only group omitted consistently from this series. A small number of individual cases were excluded for a variety of reasons. These will be discussed in the section of the report devoted to the composition of the sample. To maintain control of sampling procedures, the instructions provided that reports for all cases of definitely diagnosed coronary occlusion within the definitions provided should be forwarded to the Central Laboratory with appropriate comments by the responsible investigators regardless of gaps in information or other unusual or complicating features.

The specific instructions covering the inclusion or omission of cases read as follows: "Because of the special difficulties involved, *the analysis will omit cases dying within the first 24 hours after hospitalization;* consequently, forms for these cases need not be sent in. However, *no* other cases diagnosed as having coronary occlusion should be omitted regardless of what unusual circumstances develop. If the necessary information is lacking and cannot be secured, incomplete forms should be submitted."

When the diagnosis of coronary occlusion was established belatedly, but within the six-week period, anticoagulant therapy was instituted, provided the case had been admitted to the hospital on an odd day. The case was managed thereafter in a manner identical to that of a case which had been treated from the first day of hospitalization. If the diagnosis was made at so late a date that it was felt undesirable to administer anticoagulants, the case was reported as an odd-day case to which no anticoagulant was administered by reason of the tardy diagnosis.

The participating hospitals were urged to determine the prothrombin time on all patients for whom a diagnosis of coronary occlusion was even remotely considered so that a complete record of the plasma prothrombin times would be available should the diagnosis of coronary occlusion be made eventually.

Period over Which the Patients Were Observed

It was the intent of the Committee that each patient included in this study, irrespective of whether he was or was not treated with an anticoagulant, be observed over a period of six weeks from the date of onset of the observed attack of coronary occlusion with myocardial infarction.

While the desirability of determining what effect, if any, the use of anticoagulants would have on the ultimate prognosis is admittedly great, such a study did not appear feasible.

The decision was made to embark upon a program which would guarantee within a period of three years a total number of cases sufficient to warrant statistical analysis. The decision to follow each patient for six weeks was made because the vast majority of patients suffering an attack of acute coronary occlusion with myocardial infarction are clinically recovered from the acute attack and the infarcted area in the heart usually healed by this time.

Since it was expected that some patients would be discharged from the hospital prior to the end of six weeks, arrangements were made by the responsible physicians to obtain

adequate follow-ups on such individuals, by personal interview in the out-patient department, or through the private physician managing the particular case. In the few instances where a personal interview was impossible because of geographic or other reasons, arrangements were made for a six-week follow-up by mail or by telephone to ascertain whether or not the patient was still living, and whether or not he had suffered another coronary attack, or any thromboembolic, hemorrhagic, or other complication or sequelae In instances where a discharged patient had developed complications or sequelae of any sort, an attempt was made to obtain full information concerning the nature and circumstances of such complications.

Many patients were kept under surveillance, or were available for questioning for periods longer than six weeks, but no attempt was made by the Central Laboratory to obtain data subsequent to *forty-two days*, since the objectives of this program were to determine the effect of anticoagulant therapy on the immediate morbidity and the immediate mortality following an attack of acute coronary occlusion with myocardial infarction.

RECOMMENDATIONS REGARDING USE OF ANTICOAGULANTS

Administration of Dicumarol

It was suggested in the initial instructions to the participating hospitals that dicumarol be administered as follows:

"a. Heparin may be given for the first 48 hours or more if desired.

b. Prothrombin determinations are to be done each day

c. Dicumarol, 300 mg. daily, should be given until the prothrombin time is 30 seconds.[d]

d. Dicumarol, 100 to 200 mg. daily, should be given if the prothrombin time is between 30 and 35 seconds.

e. Dicumarol is discontinued if the prothrombin time is 35 seconds or more. Then, no drug is given until the prothrombin is again down to 30 seconds or less, after which the drug is again given cautiously in 100 mg. doses.

f. All prothrombin times are given in terms of the Link-Shapiro (undiluted) method."

As a result of experience in this study and additional experience with the use of the drug, more detailed instructions for administering dicumarol have been worked out and will be found in Appendix D.

It was cautioned repeatedly that no dicumarol should ever be ordered for a patient unless that patient's prothrombin time on that particular day was known by the prescribing physician. It was pointed out that the prothrombin time is known to rise for *several* days after a given dose of dicumarol has been received and that it does not return to normal for two to five days, or more, after dicumarol has been discontinued.

The hospitals were warned of the contraindications to the use of dicumarol although experience has shown that in many instances anticoagulant therapy can be used in the presence of certain contraindications, if administered cautiously.

It was advised that dicumarol be administered over a minimum period *of thirty* days and that it be continued for at least thirty days after the last thromboembolic episode, if the patient's course had been so complicated. This advice was emphasized when the preliminary review of the collected data on the first 800 cases[182, 183] revealed that there was a relatively high incidence of thromboembolic complications in the untreated group through the first four weeks following coronary occlusion with *myocardial* infarction.

[d] Doses actually used tended to be conservative and totalled in general between 400 and 700 mg in the first three days (See Chapter XII).

Determination of the Plasma Prothrombin Time

The original instructions to the participating hospitals requested that the patient's plasma prothrombin time be determined each day for the entire period of observation. The purpose of determining the prothrombin time each day on the control (nondicumarolized) patients was to chart, if possible, the natural course of the plasma prothrombin activity uninfluenced by dicumarol therapy following coronary occlusion with myocardial infarction. The period of observation was defined as extending through the first 42 days after the onset, *unless* a thromboembolic complication occurred during this period. When such a complication did occur, it was recommended that dicumarol be administered for a minimum period of at least thirty days after the last thromboembolic complication and that the period of observation be prolonged accordingly. However, the actual tabulations apply uniformly to the first 42 days after onset.

The request was made that when a patient had been receiving dicumarol and the dicumarol was discontinued, prothrombin times be determined each day until the prothrombin time had once again become normal. There were two reasons for this request: (1) to determine the number of days required for the prothrombin time to return to normal after the discontinuation of dicumarol therapy, and (2) to ascertain if and when patients who had been on dicumarol therapy developed thromboembolic complications following the withdrawal of such therapy.

There was one rather consistent exception to the rule of obtaining daily prothrombin times. In those laboratories where technicians were not available on Sunday or on holidays (this was the case in a number of hospitals), prothrombin determinations could be obtained only if performed by a member of the resident staff. It was felt that such determinations might be inaccurate because of the physician's unfamiliarity with the technique and his reluctance to perform a rather painstaking laboratory procedure in addition to his burden of extra duties on such days. For this reason, it was suggested that when technicians were not available, it was unnecessary and probably undesirable to delegate the prothrombin determinations to the house staff except under special circumstances.

The experience of the various hospitals as the program progressed showed that this policy was consistent with satisfactory control of the prothrombin levels. However, periods such as two-day holidays when prothrombin determinations could not be obtained over a period of 48 to 72 hours were considered more hazardous, particularly when patients entered the hospital on such days and were started on dicumarol therapy before an initial prothrombin time could be obtained.

It was recommended that the plasma prothrombin time be determined by means of the original one-stage method described by Quick, or by the Link-Shapiro modification of this method, using undiluted (whole) plasma. (The instructions describing the latter method in detail and including references to the original descriptions of both methods are reproduced in Appendix D.)

It was suggested, as an additional safeguard in the administration of dicumarol, that the plasma prothrombin time also be determined each day on 12.5 per cent dilute plasma, according to the recommendations of Link and Shapiro. It is well known that the use of dilute plasma furnishes a very sensitive guide to changes in the prothrombin activity of the plasma. The evidence of these changes is not only apt to be of greater magnitude when dilute plasma is used, but [illegible] plasma.

Overman, Newman and Wright, in the Central Laboratory, studied the daily variation in the normal prothrombin clotting time

by means of the Link-Shapiro technique and using a thromboplastin obtained from rabbit lung.[m] Daily plasma prothrombin times were determined on 25 presumably normal adults over periods of from ten to forty [illegible]

[illegible]

was obtained and the range was 12 to 18 seconds. In 813 determinations, using 12.5 per cent dilute plasma from these same subjects, a mean value of 38.6 seconds with a standard deviation of ± 2.16 seconds was obtained and the range was 32 to 42 seconds.

Since one of the factors which is most apt to produce variation in the results obtained when determining the plasma prothrombin time is the potency of the thromboplastin mixture used in the test, the hospital laboratories were advised to test for potency of the thromboplastin mixture prepared for use on any given day against the blood of two normal persons. The prothrombin times so obtained were averaged and reported as the "standard" or "control" values for the prothrombin determinations done in that particular laboratory on the given day. The hospitals were urged by the Central Laboratory to record these daily control values along with the values obtained on the blood from each patient under observation on the patient's hospital chart for the benefit of the prescribing physician. The responsible investigators were asked to record the average control value obtained by the laboratory on [illegible]

[illegible] these control values routinely is twofold. They serve first as a check on the potency of the thromboplastin being used for the determination. If the potency of a batch of thromboplastin is materially reduced so that the control values fall outside of the range ordinarily obtained in the particular laboratory, the particular batch of thromboplastin should be discarded in favor of a batch with full potency. If, however, the control value for a given day is within the normal range of 12 to 18 seconds for whole plasma and 32 to 42 seconds for 12.5 per cent dilute plasma, it is of some value to the clinician ordering dicumarol to know whether the prothrombin time for the day is relatively "slow" or "fast."

Since the temporal values tend to fan out on the prothrombin dilution curves as the degree of dilution is increased and since the values obtained when dicumarol is administered in therapeutic doses are equivalent to a dilution of the plasma to from 10 to 20 per cent of normal, a variation in the potency of the thromboplastin which produces a difference of less than four seconds in normal undilute plasma may produce a difference of 7 or 10 seconds in tests applying to cases under active anticoagulant therapy. Such a difference in temporal values represents a difference in prothrombin activity of from 5 to 10 per cent in this range of activity.

The instructions for the administration of dicumarol specified that the plasma prothrombin values be reported in terms of seconds. At the time the study was initiated, there was still confusion in the minds of some physicians as to the proper way in which to convert an observed prothrombin time (in seconds) into prothrombin activity as expressed in per cent of normal. It is generally accepted that the reduction of prothrombin activity in vivo produced by the administration of dicumarol closely approximates that produced in vitro by the dilution of normal whole plasma and that the relationship between the prothrombin time in seconds and the reduction of prothrombin activity as expressed in per cent of normal is expressed by a hyperbolic curve. Some workers have insisted until recently, however, on calculating the reduction in prothrombin activity by the formula:

$$\frac{\text{normal control prothrombin time}}{\text{observed prothrombin time}} \times 100$$

which produces a linear curve which is no

at all comparable to the hyperbolic curve, especially in the higher dilutions. The reporting of prothrombin values directly in seconds was felt to be a precaution against the use of this latter, erroneous type of calculation. These data were thereafter converted by the statistical office into seconds, having comparable meanings from one hospital to another by procedures described in Chapter XII.

Although each of the participating hospitals employed either the original one-stage method of Quick, or the Link-Shapiro modification of that method in performing the daily plasma prothrombin determinations, not all hospitals utilized the same type of thromboplastin. Commercial thromboplastins manufactured by Maltine, by Difco, or by Squibb were used according to individual preference and, in some instances, thromboplastin was prepared from rabbit brain or human brain in the hospital laboratory. In one or two instances, the thromboplastin employed initially was replaced by another product because of dissatisfaction with the original material, or its cost. There were also minor variations in the details of the technique employed by the different laboratories. These variations from the prescribed instructions led to great divergence in control values reported by the several hospitals. The manner in which this problem was handled will be discussed in Chapter XII.

The responsible investigators were requested to report in great detail instances of hyperreactions to dicumarol, including not only the amount of dicumarol administered and the prothrombin level attained, but also a review of factors which might have explained the patient's exaggerated response. The presence or absence of kidney or liver diseases, of congestive heart failure, or of pre-existing hypoprothrombinemia were of particular interest in this connection. Renal or hepatic function tests were advised in appropriate instances.

Administration of Heparin

When an adequate initial dose of dicumarol is administered to a patient, the plasma prothrombin time is not prolonged maximally for a period, usually of from 48 to 72 hours.[22, 35, 172, 325] During this interval the patient is not given maximum protection against the occurrence of thromboembolic phenomena. For this reason, the participating hospitals were privileged to administer heparin during the first few days of anticoagulant therapy to those patients for whom immediate effective anticoagulant treatment was felt imperative.

The decision whether or not to employ heparin in any given case, or in any series of cases, rested entirely with the responsible investigator at each participating hospital. Heparin was actually employed in a relatively small number of instances.

The original instructions to the participating hospitals included a request for information concerning the technique of administration and the dosage of heparin employed in each hospital. Subsequently, standardized procedures were sent to each responsible investigator as a guide to the use of heparin. It was hoped that in this way some degree of uniformity in the administration of this anticoagulant would be attained for purposes of statistical analysis. The standardized procedures recommended for the use of heparin are reproduced in Appendix D.

As Evans and others have warned,[87] when a patient under the influence of adequate amounts of heparin is placed on dicumarol, heparin must not be discontinued arbitrarily. Premature withdrawal of the heparin may permit the clotting time of the blood to return to normal before the plasma prothrombin activity has been reduced sufficiently to afford the patient full protection against intravascular clotting. Thromboembolic complications are then quite apt to occur in that interval during which neither drug is fully effective. This situation occurred in several instances in this study.

For this reason, supplementary instructions to the participating hospitals urged [illegible] of heparin to any [illegible] prolonged to a level considered therapeutically satisfactory, irrespective of the number of days which had elapsed since the institution of dicumarol therapy. It was re-emphasized in these supplementary instructions that the determination of the prothrombin time on patients receiving heparin in addition to dicumarol must be performed on specimens of blood obtained just prior to the administration of the next dose of heparin, when the clotting time of the whole blood was reduced to not more than 10 to 15 seconds, since high concentrations of heparin in the blood will prolong the plasma prothrombin time.

REPORTING PROCEDURES

Reporting of Cases to the Central Laboratory

The pertinent data on each case observed in this study were reported in great detail to the Central Laboratory on two forms designed for this purpose by the Committee. These forms were revised during the course of the study, but the changes consisted almost entirely of alterations in the spacial arrangements to provide greater convenience in the recording of data and did not, in any manner, alter the fundamental plan of the forms. For this reason, the revised form is used to exemplify both itself and the original and no particular reference need be made to the minor variations between the two.

A facsimile of this revised form appears in Appendix E and is supplemented by detailed resumes of the original instructions furnished each participating hospital at the time the initial forms were distributed. Actually, the initial instructions were followed almost immediately by a supplement in which appeared answers to questions propounded by responsible investigators as to the details of reporting certain data. For purposes of clarity, these supplementary instructions are incorporated with the originals reproduced in Appendix E. Abstracts of the supplementary instructions issued at the time the revised forms were distributed are enclosed in parentheses. It will be noted that these do not alter the basic plan of reporting.

One of these forms was filled out completely on each observed patient at the time of his discharge from the study, or at a convenient interval thereafter. Whether the form was completed by the responsible investigator, or by one of his associates, the responsible investigator was expected to certify by his signature that the case was suitable for inclusion in the study.

As the individual reports were received in the Central Laboratory, they were reviewed in considerable detail, first by the coordinator of the program and then by the statistician. In each instance where data were lacking without explanation, or where there was a conflict of fact, a discrepancy in reporting, or an incomplete clinical or laboratory evaluation, a letter was sent to the responsible investigator asking for additional data or an explanation. The defect was corrected or explained satisfactorily in almost all instances.

The reporting forms were also reviewed minutely for unrecognized evidence of thromboembolic or hemorrhagic complications, congestive heart failure, or shock, and other items of particular significance. When these were suspected from the data reported, the responsible investigator was requested to review the original records.

Reporting of Thromboembolic and Hemorrhagic Complications

The cooperating hospitals were urged repeatedly to report in great detail the circumstances surrounding the occurrence of any thromboembolic or hemorrhagic complication, irrespective of whether such complications occurred while the patient was receiv-

ing anticoagulant therapy. The information desired in such instances included:

(1) A description of the complication, its nature and location and an estimate of its severity.

(2) A list of the symptoms, signs, and ancillary evidence upon which the diagnosis was based.

(3) The date of its occurrence and the status of anticoagulant therapy and of the prothrombin time before, during and immediately after the occurrence of the complication.

(4) A discussion of the etiology of the complication, including *the evidence for and against the existence of possible predisposing* or precipitating factors.

It was emphasized that complications arise in many instances as a result of coexisting pathological conditions, perhaps unrecognized previous to the appearance of the complication and often unrelated to the patient's presenting illness. In our experience, this has been especially true when hemorrhages occur in the presence of a prothrombin time which is *not prolonged excessively* (i.e., whole plasma prothrombin time of from 30 to 50 seconds). In each instance where bleeding of any significant degree occurred, irrespective of its source, the attending physician was urged to examine the possibility that the bleeding had been primarily the consequence of a pathological condition unrelated to the presenting illness and that the hypoprothrombinemia produced by dicumarol therapy had been merely the factor precipitating the hemorrhage. Unexpected hemorrhage during anticoagulant therapy has been reported in the literature in patients with blood dyscrasias, gastrointestinal ulcerations (peptic *ulcer, ulcerative colitis, hiatal* hernia), cancer in numerous sites, focal or diffuse renal disease, and renal lithiasis. In order to ascertain promptly the presence of microscopic hematuria, hospitals were urged to perform routine urinalyses bi-weekly during the period of observation.

When hemorrhages were sufficiently severe to warrant the administration of vitamin K or fresh whole blood, the details of *this therapy were requested. Such data in*cluded the following information:

1. Vitamin K: dates of administration, preparation used, amount administered, total dose, route of administration, response observed, effect on prothrombin time.

2. Transfusions: dates of administration, blood or plasma given, amount administered, total amount given, response observed, effect *on prothrombin time.*

Reporting of Postmortem Findings

The cooperating hospitals were requested to secure postmortem examinations when possible and to study the vascular system in detail. It was felt that the major veins of the pelvis and legs should always be examined for thrombi, particularly when *pulmonary* emboli had occurred or been suspected during life.

There was no special form for the reporting of postmortem findings. Copies of the *complete autopsy protocols, including both* the gross and microscopic findings, were forwarded to the Central Laboratory by the participating hospitals as rapidly as these were available. These protocols were analyzed by means of special forms for summarizing, cross checking and classifying autopsy findings in the Central Laboratory. These complete protocols were of particular value to the staff in ascertaining in what de*tail the autopsy had been performed* and, especially, in what detail the vascular system had been studied. Some benefit was also obtained by correlating the postmortem findings with *clinical impressions, particularly* when the latter were brief or inconclusive.

Details regarding the number and extent of the autopsies performed, the extent of explanatory notes, and the *frequency* of

microscopic examinations are reported in Chapter XIII. As suspected *a priori*, there was great variation in the frequency and detail with which individual organs or systems were examined. *A failure to fully explore the vascular system undoubtedly accounts in a considerable measure for the relatively low incidence of thromboembolic phenomena in many series of autopsied cases reported in the literature.*

Coordination of the Program

The coordination of a program of this scope, conducted in 16 widely separated institutions, involved a tremendous amount of correspondence and a considerable number [illegible] A brief resume of the man- [illegible] cooperative research programs of this magnitude in the future.

Instructions to the Hospitals

Although the original instructions to the responsible investigators were detailed and thorough, they provoked a considerable number of inquiries which were answered by a set of supplementary instructions (cf. Appendix E). Further supplementary instructions were incorporated into the periodic newsletters.

Newsletters to the Hospitals

Four mimeographed newsletters were issued at irregular intervals between February 1947 and March 1948. The purposes of the newsletters were to report progress in the program, to pool information obtained by individual investigators, and to pose questions that had arisen in the course of the study.

Preliminary Statistical Reports

Preliminary statistical analyses of the gross data on deaths and thromboembolic and hemorrhagic complications were made periodically during the course of the study and were distributed to the members of the Committee. The second preliminary analysis on 800 cases was done in considerable detail and appeared as a formal report in the *American Heart Journal* and in the *Journal of the American Medical Association.*[111, 112]

Letters of Inquiry and Reply

As the report of each case observed in this study was subjected to a detailed medical and statistical review in the Central Laboratory, questions were framed for the responsible investigator concerning any sections of the report in which the statements were incomplete, inconclusive, or poorly understood. A considerable percentage of reports raised one or more queries and a few reports necessitated a considerable amount of explanation, supplementary data, or discussion. Since the responsible investigators ordinarily forwarded their completed reports in batches of several or many, it was possible to make these inquiries in periodic letters to each hospital.

In addition to the many letters of individual inquiry and answer, there were a considerable number of form letters sent out to each of the responsible investigators commenting upon or instructing the hospitals as to the handling of specific problems which promised to cause difficulty in the statistical analysis. The members of the Committee were urged repeatedly to raise questions for the purpose of improving the management of the program and expanding the coding of the reports for the final analysis.

Conferences

A conference attended by the members of the Committee and some of the other participants in the study was held in Atlantic City on June 8, 1947, shortly after the actual collecting of cases had begun. A round-table discussion permitted each responsible investigator to discuss the study in the light of his experience up to that time. Certain common problems were discussed, misunder-

standings resolved, and many suggestions were made for the improvement of the study.

Hospital Visitations

The Chairman of the Committee, or the Coordinator visited each of the participating hospitals on one or more occasions during the course of the study. The majority of hospitals were visited during the summer of 1947 at which time the management of cases under observation and the performance of the prothrombin determinations were examined critically and conversations were held with the member of the group participating in the program locally.

Many of the responsible investigators visited the Central Laboratory at The New York Hospital from time to time to discuss various aspects of the study. Such visits permitted these investigators to discuss problems in respect to the prothrombin determinations with Dr. Overman and those in respect to the collection of data and statistical analysis, with Dr. Beck. Conferences and seminars attended by the personnel in the Central Laboratory were held at frequent intervals during the entire study. Informal discussions with participating physicians were also held at the American Medical Association meeting in Chicago in June 1948.

SUMMARY

The study was designed to afford extensive statistical data adequate for a definitive evaluation of the merits of anticoagulants in the treatment of coronary occlusion with myocardial infarction. The plan provided for participation by 16 cooperating hospitals, all following the same procedures and each providing cases for both the control and treated groups. Cases admitted on odd days were to receive anticoagulant therapy in addition to conventional therapy and cases admitted on even days, conventional therapy only. Criteria for the diagnosis of myocardial infarction were outlined and it was agreed that doubtful cases and cases not surviving the first 24 hours of hospitalization were to be omitted. Procedures for the administration of dicumarol and heparin were recommended but it was understood that the attending physicians were free to adjust these procedures according to their own judgment of the needs of the patients. Daily prothrombin time determinations were to be made and reported, following, if feasible, certain specified procedures. All nonfatal cases were to be observed for a six-week period, regardless of prior hospital discharge. A detailed schedule of facts dealing with the history, treatment, clinical course and laboratory findings for each case and conforming to detailed specified instructions was required by the Central Laboratory, together with full copies of all pertinent autopsy reports. The findings reported in the remaining chapters are based on an analysis of these reports.

Assignment of Cases to Treatment Groups

IF differences between the control and treated groups are to reflect the effects of anticoagulant therapy rather than some difference unrelated to such therapy, it is of great importance that the true difference in outcome, if any, not be hidden or distorted by lack of comparability in the types of patients included in the two groups. It therefore seems necessary to present in some detail the procedures that affected the assignment of patients to the two treatment groups. This is the function of the present chapter. The following three chapters will examine, where possible, the degree to which these procedures actually resulted in comparability.

TOTAL NUMBER OF CASES STUDIED

One thousand and ninety-four cases[a] diagnosed clinically by the responsible investigators as definite attacks of coronary occlusion with myocardial infarction were observed in the sixteen participating hospitals and reported between the spring of 1946 and the summer of 1948

Sixty-three cases for whom records were submitted were omitted from the sample because they failed to meet all of the criteria necessary to qualify as "a case." The reasons for disqualification and the number of cases so disqualified are enumerated in Table 2. Both the total number of cases omitted and the numbers omitted for specific reasons were almost equally divided between patients who entered the hospitals on even days and those who entered on odd days.

The total sample used for the analysis consists, therefore, of 1031 cases of acute coronary occlusion with myocardial infarction, fulfilling the criteria defined for acceptance (see footnote a).

DEFINITION OF THE "CONTROL" AND "TREATED" GROUPS

Patients admitted to the participating hospitals on the *even days* of the month were ordinarily considered *control patients and were not treated* with anticoagulants. Exceptions to this rule were as follows: (1) even-day cases given anticoagulants after a thromboembolic complication had developed were kept in the control group and (2) even-day cases given anticoagulants for miscellaneous reasons in the absence of thromboembolic complications were transferred to the treated group.

Patients admitted to the hospitals on *odd days* were considered members of the *treated* group and were given anticoagulant therapy. Exceptions to this rule were as follows: (1) odd-day cases not given anticoagulants because of the presence of a contraindication to such therapy were retained in the treated

[a] A case was defined as a single attack of coronary occlusion with myocardial infarction diagnosed by the responsible investigator as definite on the basis of clinical evidence, not fatal *within the first* twenty-four hours of hospitalization, treated on a participating hospital service according to designated "treated" and "control" procedures, and observed medically with the *necessary records* for six weeks, if possible, following the attack. (All nonfatal cases included were followed for six weeks, except for 18 cases, all of whom were followed for at least 37 days.) A new myocardial infarction within this six-week period was counted as a thromboembolic complication, and readmission of the same case with a new myocardial infarction, after six weeks had elapsed, was counted a new case. Altogether, 1018 different individuals were studied.

group and (2) odd-day cases from whom anticoagulants were withheld for reasons other than *contraindications* were transferred to the control group.

Of the 442 patients included in the *control group* for statistical analysis, 395 were even-day cases who received no anticoagulant therapy at any time. Thirty-five were even-day cases who received anticoagulants only after the development of a thromboembolic complication. These cases were kept in the control group because they were a highly selected subgroup. To compensate for the administration of anticoagulants, estimates were prepared as to the number of thromboembolic complications, deaths and hemorrhages that would have occurred if no anticoagulants had been received and corrections were made in the findings on the basis of those estimates.[b] An additional 12 patients in the control group were odd-day cases who were not given anticoagulants for miscellaneous reasons, not including contraindications to such therapy. These cases were tabulated as control cases since they received no anticoagulants and a consistent bias in the type of case involved was not apparent.

Of the 589 patients included in the *treated group* for statistical analysis, 546 were odd-day cases who received anticoagulants according to the original plan. An additional 31 were even-day cases who received anticoagulants preventively as an exception (e.g., "at the request of a private physician," etc.) at least two days before a thromboembolic complication developed (or developing no complications). These were tabulated as treated cases since they actually received anticoagulants and there was little evidence of selection or bias in this group. Twelve others were odd-day cases not receiving anticoagulant therapy because of medical contraindications. These were kept in the treated group and no corrections were made since these omissions were the result of disadvantages inherent in anticoagulant therapy. The reasons reported by the hospitals for the making of these various exceptions

TABLE 2

OMISSIONS: Number of Cases Omitted from the Sample for Whom Records Were Submitted, by Reason for Omission

Reason for Omission	Number of Cases Omitted		
	Total Omitted	Cases Admitted on Even Days	Cases Admitted on Odd Days
Case observed for less than 37 days	20	9	11
Diagnosis of coronary thrombosis in doubt or changed under observation	13	6	7
Patient lived less than 24 hours after hospital admission	12	7	5
Patient not observed on designated treated and control basis	12	4	8
Patient admitted to a nonparticipating service and later transferred; records inadequate, or procedures incorrect	2	1	1
Patient transferred to another hospital within 42 days; necessary records not obtained	2	1	1
Case admitted more than 42 days after attack	1	1	—
Coronary occlusion not recognized until autopsy	1	—	1
Total cases omitted	63	29	34

[b] These corrections added 7.5 deaths (1.7 per cent) to the control patients reported as dying, and 12 9 complications (2 9 per 100 cases) to the number of complications reported for the control group. Hemorrhages in the control group were corrected by omitting from the control group 5 episodes of bleeding under anticoagulants believed due to, or aggravated by, anticoagulants. For explanation of method used in estimating these corrections, see Appendix B.

and the number of cases involved in each category are given in Appendix F, Table 1.

While the number of exceptions apparent from these listings in Appendix F, Table 1 may appear large in aggregate, it must be considered that a procedure for randomizing the two groups was selected that made exceptions more than usually obvious. If the usual method of alternating cases in clinical experiments; namely, the application of

TABLE 3

COMPOSITION OF TREATMENT GROUPS: Number, Percentage, and Average Age of Cases Who Were Included in the Control and Treated Groups on the Basis of Day of Admission and/or Treatment Received

Groups and Subgroups	Number of Cases[a]	Percentage of Cases	Average Age
Control Group.			
Cases admitted on even days and receiving no anticoagulants[b]	395	38.3	59.9
Cases admitted on odd days and receiving no anticoagulants for miscellaneous reasons not involving contraindications[c].	12	1.2	57.5
Cases admitted on even days and receiving no anticoagulants until one or more complications developed and given anticoagulants thereafter	35	3.4	58.6
Total control group	442	42.9	59.7
Treated Group:			
Cases admitted on odd days and receiving anticoagulants routinely	546	52.9	58.6
Cases admitted on even days and receiving anticoagulants preventively for miscellaneous reasons at least two days before a [illegible]	31	3.0	61.5
[illegible]	12	1.2	64.6
Total treated group	580	57.1	59.0
Total sample	1031	100.0	59.3

[a] "Number of Cases" (sometimes referred to as "case counts") refers to the number of individual attacks of coronary occlusion with myocardial infarction studied and not the number of different patients of given ages studied. Cases are classified [illegible] mission for the [illegible]

[illegible] dicumarol the day before death, (4) one re[illegible] days, and (5) one received a total of 2 doses (400 [illegible] these patients are tabulated throughout as receiving no anticoagulants [illegible] of simplification, made for these very minor exceptions [illegible] and no corrections have been

[d] One patient in this group received a single dose of dicumarol (300 mg.) only.

CASES INCLUDED IN CONTROL AND TREATED GROUPS

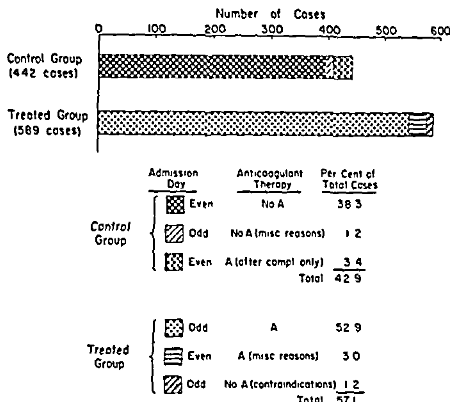


Figure 1. CASES INCLUDED IN CONTROL AND TREATED GROUPS: Number and percentage of cases in the total sample belonging to various treatment and admission day subgroups and the treatment groups to which they were assigned for purposes of the statistical analysis.

specialized treatment to every other case received in sequence, had been used instead of the odd- and even-day procedure, only those exceptions that were recognized and voluntarily reported by the attending physician specifically as exceptions could have been identified in the statistical analysis. Probably under such circumstances, the number of exceptions would have appeared much lower, but a hidden bias of unknown type doubtless would have occurred in the sampling for which no corrections could have been made. While some hidden manipulation of admission dates apparently occurred occasionally in the present study (see discussion on page 9), the amount of distortion has been greatly reduced and analytic precision increased by the fact that cases properly belonging to the control group —frequently severe cases—who received anticoagulants as exceptions could be identified. Such cases could then be kept in the control group with appropriate corrections rather than classified unawares in the treated group with consequent uncorrectable loss of comparability. The switches purposefully made between groups (see above listing) in instances where no selective influence was obvious do not appear to have had any important effect on the comparability of the two groups.*

* An examination of the composition of the control and treated groups before and after these various switches had been made indicated that differences between the two groups in the percentage of cases showing 30 selected traits related to sample composition, medical history, severity of illness, and clinical course were in no instance increased more than two percentile points by these switches. In 15 of the 30 traits examined, the two groups became more rather than less comparable

The procedures here described for defining the control and treated groups were developed after a full consideration of the issues involved and possible alternatives. In general, the principle applied was that improvement of the purity of the treatment groups by reassignment was to be permitted only when the original exception in treatment appeared to have been made on the basis of factors probably not directly correlated with the major outcomes under study; namely, deaths, thromboembolic complications, and hemorrhages. Impurities in treatment which could not be corrected under this procedure were corrected by means of approximate statistical estimates, the amounts of which are reported by subcategories in every Appendix F table where relevant. The major findings as they would have been if alternative definitions of the control and treated groups had been used are given in Appendix F, Table 2, together with an explanation of the advantages and disadvantages of each alternative procedure.

SIZE OF TREATMENT GROUPS

The control group as constituted by the procedure actually adopted consists of 442 cases, or 42.9 per cent of the total sample of 1031 cases. The treated group consists of 589 cases, or 57.1 per cent of the total sample of 1031 cases. These data are tabulated in Table 3, along with the average ages of the cases in each group and subgroup, and are presented graphically in Figure 1. All co-operating hospitals contributed cases to both the control and treated groups and the distribution of the control and treated groups among the various hospitals did not differ significantly when tested [illegible]

TABLE 4

HOSPITALS PARTICIPATING: Number and Percentage of Cases in the Total Sample Contributed by Each of the Participating Hospitals

Hospital	Cases Contributed to Total Sample: Number	Per Cent of Total
Bellevue, New York	49	4.7
Beth Israel, Boston	57	5.5
Cincinnati General	101	9.8
Cleveland City	23	2.2
Henry Ford, Detroit	126	12.2
Jackson Memorial, Miami	43	4.2
Lakeside, Cleveland	102	9.9
Massachusetts General, Boston	26	2.5
Michael Reese, Chicago	130	12.6
Mount Zion, San Francisco	45	4.4
The New York Hospital, New York	69	6.7
Pennsylvania, Philadelphia	40	3.9
Peter Bent Brigham, Boston	47	4.6
Rhode Island, Providence	115	11.2
San Francisco, San Francisco	25	2.4
Veterans Administration, Bronx, New York	33	3.2
Total cases	1031	100.0

Four hundred and seven, or 92.1 per cent of the 442 cases in the control group, did not receive anticoagulant therapy,* but 35, or 7.9 per cent of the cases in this group of 442 did receive anticoagulants after the development of one or more thromboembolic complications. Four hundred and eighty-four, or 82.2 per cent of the cases in the treated group received dicumarol alone; 91, or 15.4 per cent, received some heparin in addition to dicumarol; and 2, or 0.3 per cent, received heparin alone. Twelve, or 2.0 per cent, of the cases in the treated group received no anticoagulants because of renal or liver disease, or because of the risk of [illegible]

as a [illegible]
the [illegible]
the [illegible]
cat [illegible]
gro [illegible]
ing [illegible]
gro [illegible] Appendix F, Table 2.

[4] For this reason and for other reasons listed in footnote h on page 300, it was considered permissible to [illegible] tals and a [illegible] single universe. [illegible] samples from a

* Six patients receiving anticoagulants for one or two days only are included in this group since the amounts received and other circumstances did not fulfill the minimum criteria for therapy. See footnotes b and c in Table 3.

SOURCES OF CASES BY PARTICIPATING HOSPITALS

The number and percentage of cases in the total sample contributed by each of the participating hospitals are presented in tabular form in Table 4 and graphically in Figure 2. Three hospitals, Michael Reese in Chicago, Henry Ford in Detroit, and Rhode Island in Providence, each contributed more than 10 per cent of the total cases observed. On the other hand, three hospitals, Massachusetts General in Boston, San Francisco City and County, and Cleveland City, each contributed 2.5 per cent or less of the total cases observed. The numbers contributed to the control and treated groups by each hospital are given in Appendix F, Table 33. There was no statistically significant[f] difference between the control and treated groups in the distribution of cases among the participating hospitals.

Since the number of patients contributed bears no relation to the size, patient load, or medical services of that hospital, a brief explanation for this discrepancy is perhaps indicated. All hospitals participating in this study did not initiate the program at the same time. The delay, which extended in some instances to a matter of months, depended upon purely local circumstances and did not, as far as we can tell, have any influence on the conduct of the study once this was begun. In one instance at least, that of the Veterans Hospital in the Bronx, New York, the hospital did not join the program until it had been underway elsewhere for a period of some months. In two other instances, namely Rhode Island and Cincinnati, alternate series had already been initi-

[f] *The term "statistically significant" and the related term "not statistically significant" are defined in Appendix C.*

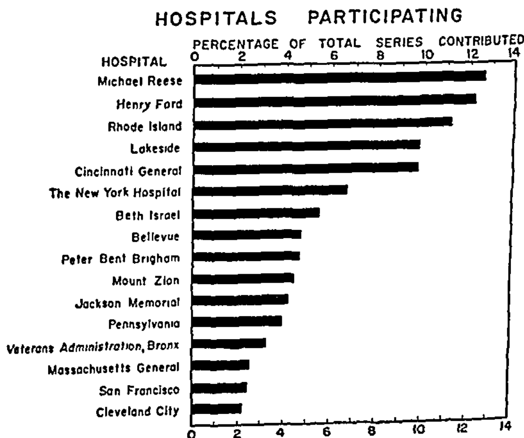


Figure 2. HOSPITALS PARTICIPATING: Percentage of the total sample contributed by each of the participating hospitals.

ated independently and were later merged with this series.

In several instances, as for example, at Bellevue Hospital and at San Francisco City and County Hospital, the medical services are divided, insofar as staff and supervision are concerned, between two or more medical schools and only the services of one institution participated in this study. In at least one hospital, Massachusetts General, the supervision of the medical service is rotated periodically and participation in the program was intermittent, depending upon the willingness of the chief of service to permit the use of anticoagulants according to the plan of the study during his tenure.

In hospitals where most beds or all beds are private, difficulty was encountered from time to time in observing the alternate-day rule for treating or not treating patients with anticoagulants. Despite prior agreement among staff members that the alternate-day rule would be observed, some private physicians were unwilling in certain instances to give, or to withhold, the anticoagulant. This defection accounts in part for the necessary transfer of cases from one group to another. It undoubtedly led to the exclusion of an occasional case from the list of patients reported by the particular participating hospital although a report of all cases, regardless of exceptions, was urged.

SUMMARY

This brief chapter supplements the preceding one by describing how the basic procedures outlined for the study worked out in practice. It lists the cases discarded from the study and the reasons for omission. It describes how the cases were finally assigned to treatment groups and the methods used to handle the problems created by occasional exceptions made in the alternate-day method of selecting cases for treatment. In addition, the contribution of each participating hospital to the sample is indicated. The total control group thus constituted consisted of 442 cases and the total treated group, of 589 cases. Whether these two groups were actually composed of comparable cases is considered in the three chapters immediately following.

SOURCES OF CASES BY PARTICIPATING HOSPITALS

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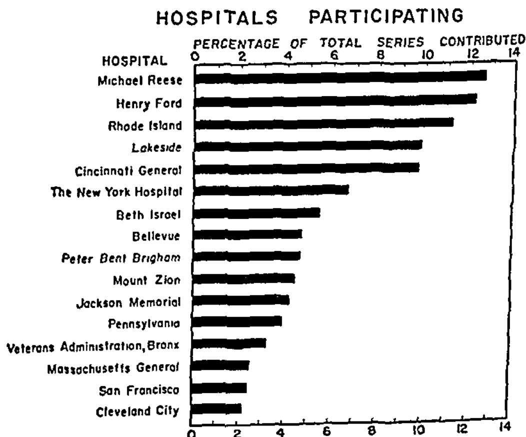


Figure 2. HOSPITALS PARTICIPATING: Percentage of the total sample contributed by each of the participating hospitals.

as compared with 75 per cent in the series of cases reported by Mintz and Katz.

Sex

There were 789 men (76.5 per cent) and 242 *women* (23.5 per cent) in this series, a *ratio* of 3.3 males to 1 female. The percentage of males and females and the sex ratios by decades are tabulated in Table 5 and presented graphically in Figure 5. Males predominate in each decade through the eighth, but the ratio falls rapidly from the extreme of 24:1 in patients 30 to 39 years of age to a ratio of 1.7:1 in patients 70 to 79 years of age. The sex ratio is about 1:1 among patients 80 years or older.

The age distribution of all cases and of males and females in the control and treated groups can be compared in Tables 8, 9, and 10 and graphically, in Figures 6 and 7. Actual counts for each group appear in ppendix F, Table 3. In general, the two roups are closely comparable.

For all cases, the greatest difference in percentile points between the control and treated groups occurs at the decade 70 to 79 years and is only 3.7 points. When the males are considered alone, the greatest difference occurs in the decade 50 to 59 years and is 6.9 percentile points. With the females, the maximum discrepancy is also in the decade 50 to 59 years and is 9.3 points.

The ratio of men to women in various series of cases of myocardial infarction reported in the literature varies from the 13:1 reported by Parkinson and Bedford[177] to the [illegible]

and Jaffe observed that the ratio of male to female reported in the literature varied from 13:1 to 3:1. Mullins,[151] in a series of 400 cases, found a ratio of 3:1. Hedley,[84] Bean,[14] Rosenbaum and Levine,[204] and Rathe[188] reported ratios similar to the 2.2:1 reported by Mintz and Katz.

Myocardial infarction is being recognized with increasing frequency in women, but is

TABLE 5

AGE AND SEX COMPOSITION OF THE TOTAL SAMPLE: Number and Percentage of All Cases and of Males and Females in the Total Sample in Various Age Groups and the Sex Distribution and Sex Ratio by Age Groups

Age Group	Number of Cases[a]			Percentage of Cases			Percentage Male and Female in Each Decade		Sex Ratio—Number of Males per Female
	Both Sexes	Male	Female	Both Sexes	Male	Female	Male	Female	
20–29	1	1	—	.1	.1	—	—[b]	—[b]	—[b]
30–39	25	24	1	2.4	3.1	.4	*96.0*	*4.0*	*24.0*
40–49	166	145	21	16.1	18.4	8.7	87.3	12.7	6.9
50–59	370	313	57	35.9	39.7	23.6	84.6	15.4	5.5
60–69	305	206	99	29.6	26.1	40.9	67.5	32.5	2.1
70–79	142	90	52	13.8	11.4	21.5	63.4	36.6	1.7
80–89	19	9	10	1.8	1.1	4.1	*47.4*	*52.6*	.9
Age unknown	3	1	2	.3	.1	.8	—[b]	—[b]	—[b]
All ages	1031	789	242	100.0	100.0	100.0	76.5	23.5	3.3
Average age	59.3	57.9	63.9	—	—	—	—	—	—

Note: *Italics are used when percentages and ratios quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] For definition of a "case," see footnote a, Table 3.

[b] Not computed since there were less than 10 cases in the sample.

CHAPTER IV

General Characteristics of the Sample

EXAMINATION of the comparability of the control and treated groups is undertaken in the present and two following chapters. The present chapter deals only with selected characteristics of the patients prior to the onset of the attack studied. Data regarding their age, sex, race, geographic residence, weight, and past medical history are reviewed. The next two chapters will deal in a similar fashion with the characteristics of the attack and the course of the illness. The data used for assessing comparability are also used throughout to reveal some of the characteristics of persons who develop coronary thrombosis with myocardial infarction and for comparisons of the sample with other series.

AGE AND SEX

The composition of the entire sample of 1031 cases by age and sex is shown numerically and in percentages in Table 5. The age distribution by decades for the total sample and for males and females separately is presented in Figure 3.

Age

As is readily evident, the numbers of patients in each decade of age from the fifth through the eighth decades were sufficient to permit analyses of most types of data by decade of age. *The numbers of patients in the fourth and ninth decades were not sufficient for sound statistical treatment and are omitted in most graphs giving data by age.* This point must be kept in mind in subsequent sections of this report where the material is discussed according to age groups by decades.

The average age of all patients in the series was 59.3 years, that for the males, 57.9 years, and that for the females, 63.9 years. These figures compare closely with those found by Mintz and Katz[152] in their study of 572 cases of recent myocardial infarction, but reveal that this series represents a somewhat older group of patients than those studied by Master, Dack and Jaffe.[135] The comparative figures are presented in Table 6.

The age distribution of the entire sample is compared with similar data from certain large series of cases of myocardial infarction reported in the literature in Table 7 and in Figure 4.

The peak of the curve for this series occurs in the sixth decade. This is similar to the findings of Willius,[245] of Master, Dack and Jaffe,[135] and of Doscher and Poindexter,[57] both in their own material and in that collected from the literature by them. Mintz and Katz,[152] however, observed a peak in the seventh decade. Our series compares with that of Mintz and Katz in that the peaks by sex fall in the sixth decade for men and the seventh decade for women. Very similar results have been reported by other observers.

Our material reflects the generally accepted impression that from 60 to 70 per cent of all myocardial infarctions occur in patients between the ages of 50 and 70 years. In this series, 65.8 per cent of the men suffered their current attack between the ages of 50 and 70 years, as compared with 62.5 per cent in the series of cases reported by Mintz and Katz.[152] Sixty-four and one-half per cent of the women suffered their current attack between the ages of 50 and 70 years

cases were from hospitals in New England, the Middle Atlantic states or the Middle West. Moreover, all of the participating hospitals are located in large urban centers and doubtless serve largely urban and suburban residents. Since similar studies have not been conducted as yet for rural areas, it is not possible to evaluate what effect, if any, this selection of cases had on the general findings. Since the composition of the control and treated groups did not differ significantly as far as participating hospitals were concerned, the urban-rural and geographic distribution of the total sample does not affect the comparability of these two groups.

TABLE 6

AVERAGE AGES OF CASES IN THREE SERIES. Average Ages of Patients at the Time of Their Current Attack of Coronary Occlusion with Myocardial Infarction in Three Series, by Sex

Series	Number of Cases in Series	Average Age		
		Both Sexes	Males	Females
This Series	1031	59.3	57.9	63.9
Mintz & Katz[13]	572	60.4	58.4	62.4
Master, Dack & Jaffe[14]	500	55.0	54.7	56.0

RACE

Almost all (95.5 per cent) of the 1031 cases in this study were reported as "White." Only 3.5 per cent were Negro. In ten instances, the race was not reported and could not be determined subsequently. Comparisons of the control and treated groups showed that 5 per cent of the control group and 2 per cent of the treated group were Negro.

The occupations and other social and economic characteristics of the patients who comprised this series were not determined in collecting the information on which this report is based.

WEIGHT

The weights, prior to the current illness, of about two-thirds (68.5 per cent) of the patients in the sample were ascertained and reported along with their heights and ages. The weights of the remaining patients were

TABLE 7

AGE DISTRIBUTIONS IN SEVERAL SERIES OF MYOCARDIAL INFARCTION: Percentage of Cases in Various Age Groups in This Series and in Several Series of Acute Coronary Occlusion with Myocardial Infarction Reported in the Literature

Age Group	Percentage of Cases					
	This Series	Mintz and Katz[13]	Willius[15]	Master, Dack, & Jaffe[14]	Doscher & Poindexter[11]	Combined Reports[a][11]
20–29	.1	—	—	—	—	—
30–39	2.4	3.8	1.6	7.8[b]	4.6	5.1
40–49	16.1	15.9	17.0	21.0	21.3	19.7
50–59	35.0	32.7	40.0	35.6	38.9	33.9
60–69	29.6	33.6	31.9	28.3	27.1	31.4
70–79	13.8	12.8	8.1	7.2	8.2	10.2
80–89	1.8	1.2	1.4	—	—	—
Age unknown	.3	—	—	—	—	—
	Number of Cases in Series					
All ages	1031	572	370	500	414	2982

[a] From 15 series collected from the literature by Doscher & Poindexter.[11]
[b] Includes patients 27 through 39 years inclusively.

extremely uncommon in women in the first three decades of life. Infarction apparently occurs later in life in women than in men and the number of women hospitalized for attacks does not approach that of men until after the age of 60 years.

Other possible measures for age and sex comparisons also fail to reveal differences of consequence between treatment groups. The average age of patients in the control group was 59.7 years and in the treated group, 59.0 years. The average age of males in the control group was 58.7 years and in the treated group, 57.3 years. The average age of females in the control group was 63.2 years and in the treated group, 64.3 years. Seventy-eight per cent of the patients in the control group and 75 per cent of those in the treated group were male. The sex ratios (male-female) in the two groups were thus 3.6:1 and 3.0:1 respectively.

GEOGRAPHIC AREA

Table 4, page 23, previously presented in Chapter III to indicate the number of cases contributed by each participating hospital, can be utilized likewise to describe the geographic areas represented by the sample. *Analysis of the sample in this fashion indicated that although the south and far west were represented, 89 per cent of the tota*

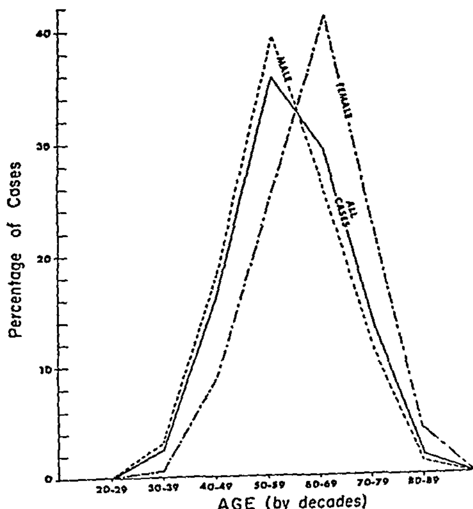


Figure 3. AGE, BY SEX: Percentage of cases in the total sample and percentage of males and females in various age groups.

not reported and were presumably unobtainable either because the patient did not know his recent weight, or because he was too ill to be questioned on this point.

It is recognized that the weights quoted by the patients are apt to vary somewhat from their actual weights, but it is doubtful if such variations are greater than a few pounds. Since weights prior to the illness were requested, it is probable that those reported were higher than the actual weights since many patients would have weighed themselves while clothed and before weight loss had occurred as a result of the present illness.

These recorded weights for each patient were compared with the average for his or her height, age, and sex, and the percentage by which it exceeded or fell short of thit average was computed from standard weighs tables for the general population supplied by the Metropolitan Life Insurance Company. Heights and weights at ages past 60 were based upon averages given for ages 55 to 59 since standard weight tables do not extend beyond that age.

The number of cases exceeding and those falling short of the standard weights (i.e., average weights for persons of similar age and height in the general population) in the total sample and in the control and treated groups was tabulated according to increments of 10 per cent above or below the standard weight. The findings appear in Tables 11 and 12, Appendix F, Table 4, and Figure 8.

In the total sample, 28 per cent of those whose weight was known were less than 10 per cent above the standard weight and 30 per cent were less than 10 per cent below the standard weight. These two groups combined

AGE, BY TREATMENT GROUPS

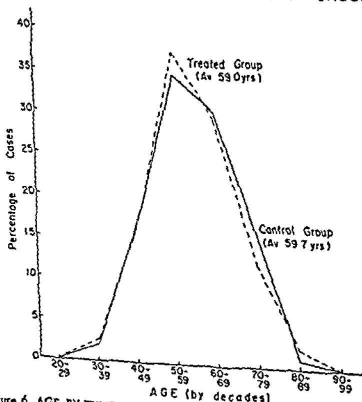


Figure 6. AGE, BY TREATMENT GROUPS: Percentage of control and treated cases in various age groups.

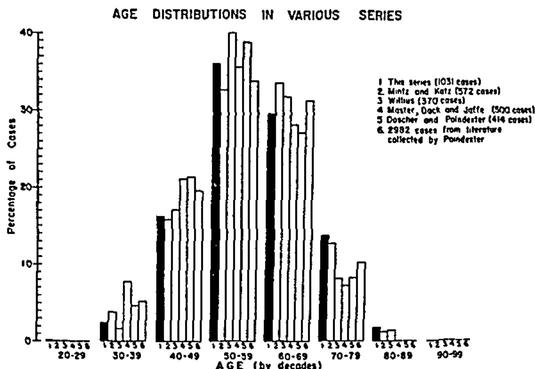


Figure 4. AGE DISTRIBUTIONS IN VARIOUS SERIES: Percentage of cases in the total sample in various age groups in this series and several other series of coronary occlusion with myocardial infarction reported in the literature.

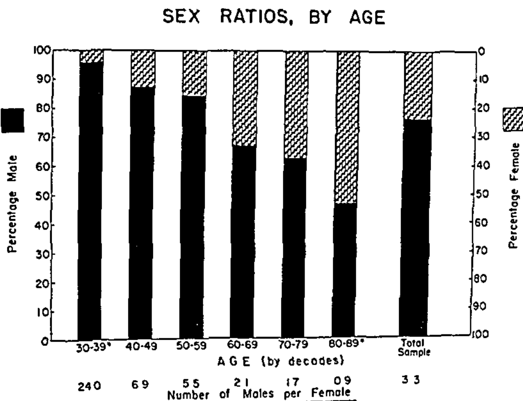


Figure 5. SEX RATIOS, BY AGE: Percentage of males and females in the total sample and number of males per female, by age.

(57 per cent) have been designated arbitrarily as within "normal range." Twenty-two per cent of those whose weights were reported were 10 per cent or more above the standard weight and were considered "overweight." About the same proportion (21 per cent) were 10 per cent or more below the standard weight and were considered "underweight."

The percentages of cases overweight, underweight, and within the normal range in the total sample and in the control and treated groups when compared by decade of age as in Table 12 are found to correspond closely.

The percentages in the *total* sample of patients in age groups 40 to 79 falling into the "normal range" and into the two extremes ("overweight" and "underweight") are projected graphically in Figure 9. It is evident that the percentage of patients who were "overweight" was highest in the fifth decade and declined slowly, but *continuously* thereafter. The opposite occurred in the case of underweight. The percentage of patients who were "underweight" was lowest in the fifth decade (about one-tenth), increased to about a fifth of the total in the sixth and seventh decades and a third in the eighth.

The meaning of this decline in the percentage of patients overweight and the comparable increase in the percentage underweight is not clear. Some degree of weight loss occurs with the development of senility. [illegible] mal decrease in the average weights in these older age groups and would be removed if correct norms were available. Whether there is a greater weight loss in patients with clinical disease of the coronary arteries than among other persons in these age groups is not known. Since physicians often recommend diets low in fat and in total calories in such cases, some weight loss might be expected.

The data on weight are also pertinent to the assertion frequently made that obesity predisposes man to the occurrence of coronary occlusion with myocardial infarction. White states—"Coronary heart disease is also common in obesity, and acute coronary thrombosis occurs more frequently in persons who are heavy than in persons who are lean.[241]" Yater et al.,[245] in a study of coronary artery disease in young men eighteen to thirty-nine years of age, observed that, while many of the men appeared to be overweight at the time of death, or of acute myocardial infarction, when the factor of obesity was investigated, it was found that the weight of these men corresponded to the average weight of all inductees and that during their Army careers they gained weight almost in the same relative degree as did other soldiers. The weight gain of those who died paralleled that of the average soldier more closely than that of the survivors, in whom there was a slight tendency to be overweight. The authors conclude, therefore, that obesity cannot be said to be

TABLE 10

AGE OF FEMALES, BY TREATMENT GROUPS · Percentage of Cases of Various Ages among Females in the Total Sample and in the Control and Treated Groups, and Average Age, by Treatment Groups

Age Group	Percentage of Cases		
	Total Sample (242 Females)	Control Group (96 Females)	Treated Group (146 Females)
Under 40	4	—	.7
40-49	8 7	9 4	8.2
50-59	23 6	29 2	19.9
60-69	40 9	37 5	43.1
70-79	21 5	22.9	20.5
80-89	4 1	1 0	6.2
Age unknown	.8	—	1.4
All ages	100.0	100 0	100.0
	Average Age		
Total cases	63 9	63.2	64.3

AGE, BY SEX AND TREATMENT GROUPS

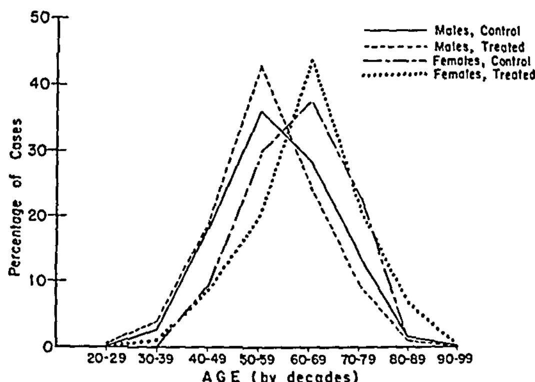


Figure 7. AGE, BY SEX AND TREATMENT GROUPS: Percentage of control and treated cases in various age groups, by sex.

TABLE 8

AGE, BY TREATMENT GROUPS: Percentage of Cases in the Total Sample and in the Control and Treated Groups of Various Ages, and Average Age, by Treatment Groups

Age Group	Percentage of Cases: Total Sample (1031 Cases)	Control Group (442 Cases)	Treated Group (589 Cases)
Under 40	2.5	2.0	2.9
40–49	16.1	16.3	16.0
50–59	35.9	34 4	37.0
60–69	29.6	30.1	29.2
70–79	13.8	15.9	12.2
80–89	1.8	1.1	2.4
Age unknown	.3	.2	.3
All ages . .	*100 0*	*100.0*	*100.0*
Average Age			
Total cases.	59.3	59.7	59 0

TABLE 9

AGE OF MALES, BY TREATMENT GROUPS: Percentage of Cases of Various Ages among Males in the Total Sample and in the Control and Treated Groups, and Average Age, by Treatment Groups

Age Group	Percentage of Cases: Total Sample (789 Males)	Control Group (346 Males)	Treated Group (443 Males)
Under 40	3.2	2.6	3.6
40–49	18.4	18.2	18 5
50–59	39 7	35.8	42.7
60–69	26.1	28.0	24 6
70–79	11 4	13.9	9.5
80–89	1 1	1.2	1.1
Age unknown	.1	3	—
All ages .	100.0	100 0	100.0
Average Age			
Total cases.	57.9	58.7	57.3

THE PAST MEDICAL HISTORY OF THE PATIENTS

An attempt was made to obtain from each patient information sufficient to ascertain whether or not certain conditions had been present, or had occurred prior to the current attack of coronary occlusion with myocardial infarction. These conditions were, in general:

1. Pre-existing heart disease or the consequences thereof.
2. Cardiovascular conditions which might indicate a predisposition to coronary occlusion with myocardial infarction.
3. Conditions which are known sometimes to modify the response of the patient to anticoagulant therapy.
4. Miscellaneous non-cardiovascular conditions which are thought to occur commonly in patients with coronary artery disease or whose presence may contribute to the morbidity and/or mortality of patients with coronary occlusion.

This information was obtained ordinarily by questioning the patient or his family. It was confirmed or elaborated in some instances from existing hospital records relating to the past medical history of the patient and in many instances by the observation of the patient during the current illness. The validity of the information is, in general, similar to that in the past medical history obtained from patients who enter the hospital suffering from any serious acute illness.

TABLE 12

OVERWEIGHT AND UNDERWEIGHT, BY TREATMENT GROUPS: Percentage of Cases Overweight, Underweight, and within Normal Range in the Total Sample and in the Control and Treated Groups, by Age

Treatment Group	Percentage of Cases[a]						
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89
	10% or More Overweight						
Total sample	22.4	*17.7*	28.9	24.8	21.6	11.9	*10.0*
Control group	23.2	—[b]	26.7	27.0	22.1	15.2	—[b]
Treated group	21.8	*25.0*	30.7	23.5	21.1	8.7	—[b]
	Within Normal Range						
Total sample	57.1	*58.8*	61.7	55.7	58.2	54.4	*40.0*
Control group	56.0	—[b]	64.4	56.0	60.0	41.3	—[b]
Treated group	57.9	*61.6*	59.6	55.6	56.9	67.4	—[b]
	10% or More Underweight						
Total sample	20.5	*23.5*	9.4	19.5	20.2	33.7	*50.0*
Control group	20.8	—[b]	8.9	17.0	17.9	43.5	—[b]
Treated group	20.3	*15.4*	9.7	20.9	22.0	23.9	—[b]
	Number of Cases of Known Weight						
Total sample	706	17	107	262	218	92	10
Control group	293	4	45	100	95	46	3
Treated group	413	13	62	162	123	46	7

Note: *Italics are used when percentages quoted have less than 50 cases as a base since chance factors render such rates particularly unstable.*

[a] Percent...

an etiological factor of any importance, at least among their young subjects.

Our data, likewise, do not support a contention that obesity is a factor of importance in the occurrence of coronary thrombosis with myocardial infarction at all ages. If cases of exactly standard weight are excluded and the remaining cases are divided into those above and those below the standard weight, only during the fifth and sixth decades do the percentages of persons with weights above the standard predominate, by 15.9 percentile points and by 6.9 percentile points respectively. If those patients whose weights are within ten per cent of the standard are considered to have normal weight, the percentage of patients overweight again is conspicuously in excess only during the fifth and sixth decades, by 19.5 percentile points and by 5.3 percentile points respectively. In the seventh decade, the clear preponderance of overweight patients with coronary occlusion and myocardial infarction has been lost. Thus obesity may play a significant role only during those decades of middle life when it is apt to be accompanied by hypertension, hyperlipemia and prematurely advanced atherosclerosis.

TABLE 11

OVERWEIGHT AND UNDERWEIGHT IN THE TOTAL SAMPLE: Percentage of Cases Overweight, within Normal Range, and Underweight in the Total Sample, by Age

Degree of Overweight or Underweight[a]	Percentage of Cases						
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89
30% or more overweight..	3.4	—	6.5	4.6	2.3	—	—
20–29% overweight	5.7	*11.8*	5.6	5.3	5.5	5.4	*10.0*
10–19% overweight	13.3	*5.9*	16.8	14.9	13.8	6.5	—
Total 10% or more overweight	22.4	*17.7*	28.9	24.8	21.6	11.9	*10.0*
Less than 10% overweight[b] .	27.5	*29.4*	29.9	29.4	27 5	20.7	*10.0*
Less than 10% underweight . .	29.6	*29.4*	31.8	26.3	30.7	33.7	*30.0*
Total within normal weight range.	57 1	*58.8*	61.7	55.7	58.2	54.4	*40.0*
10–19% underweight.. ..	14.9	*23 5*	6.6	15 3	13.8	22.8	*30.0*
20–29% underweight .	4.9	—	2.8	3.8	5.5	8.7	*20.0*
30% or more underweight .	.7	—	—	.4	.9	2.2	—
Total 10% or more underweight	20.5	*23.5*	9.4	19.5	20.2	33.7	*50.0*
Total cases of known weight ..	100.0	*100.0*	100.0	100 0	100.0	100.0	*100.0*
	Number of Cases of Known Weight						
Total cases...	706	*17*	*107*	262	218	*92*	*10*

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] [illegible] for the general population, sup- [illegible]

10.0–19 9 per cent, etc.

[b] Seventeen cases with weights exactly equal to standard weights are included here

by a physician, or when he described attacks of precordial pain which the attending physician interpreted as angina.

Among patients from whom information concerning angina was obtained, the syndrome had occurred in 51 per cent of the total sample, 52 per cent of the control group, and 50 per cent of the treated group. The difference is not statistically significant. No attempt was made to analyze the degree of severity of the angina, the frequency of attacks, circumstances in which attacks were precipitated, or the total duration of the syndrome.

According to the literature, from 20 to 75 per cent of patients suffering a myocardial infarction are reported to have experienced angina pectoris prior to the occurrence of the infarction. Mintz and Katz[151] found that 72.9 per cent of their 572 patients had experienced angina pectoris prior to the observed attack of myocardial infarction and that there was no difference in the incidence of angina by sex, or by location of the infarction. Willius[244] reported that 22.4 per cent of his patients had a previous history of angina.

Doscher and Poindexter[41] observed that 33.3 per cent of the 414 patients in their series gave a convincing history of angina which had existed for at least one month before the myocardial infarction was observed. The incidence among their 334 male patients was 33.8 per cent and among their 80 female patients, 31.3 per cent, a similarity which agrees with the findings of Willius and of Mintz and Katz. Among 3315 cases reported in sixteen series in the literature, Doscher and Poindexter[41] found that 44.0 per cent had experienced angina pectoris at some time prior to the observed attack of myocardial infarction.

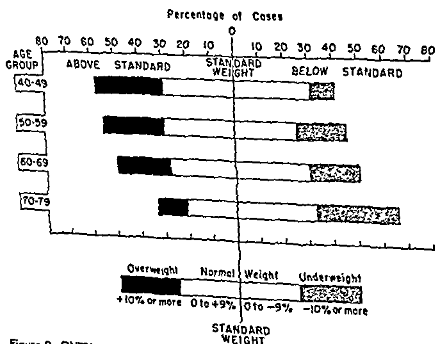


Figure 9. OVERWEIGHT AND UNDERWEIGHT, BY AGE. Percentage of cases in the total sample overweight, underweight, and within normal weight range, by age.

In many instances information regarding a particular point was lacking, or its value questionable. In those instances where the record was insufficient to make possible a definite statement that the condition was or was not present, the case was omitted from the tabulation and subsequent computations. Thus percentages throughout are based on the total number of cases for whom reports on a given condition are available. There was supporting evidence in the form of at least minimal explanatory notes in 49 per cent of the entries for conditions stated to have been present in the past medical history. Some doubt was expressed by the reporting physician in only about 0.5 per cent of all conditions which are included in the tabulations.

The number of patients in the total sample and the percentages of patients with a known medical history reporting various conditions in their medical histories are tabulated in Table 13.

The number and percentage of patients in the control and treated groups reporting various conditions in their medical histories are tabulated in Table 14.

Each condition is discussed separately in the sections which follow. The relation of these various conditions to mortality is discussed in Chapter XI.

Pre-existing Heart Disease and the Consequences Thereof

Anginal Syndrome

Angina pectoris was the condition most commonly reported in the past medical histories of the patients in this series. Angina was recorded as present when the patient stated that he had experienced attacks which had been previously diagnosed as "angina"

WEIGHT, BY TREATMENT GROUPS

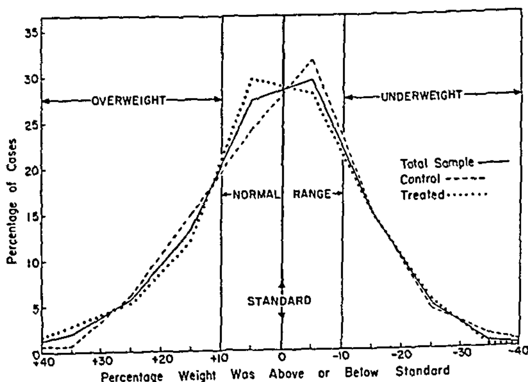


Figure 8. WEIGHT, BY TREATMENT GROUPS: Percentage of cases in the total sample and in the control and treated groups overweight, underweight, and within normal weight range.

TABLE 14

MEDICAL HISTORY OF THE CONTROL AND TREATED GROUPS: Number and Percentage of Cases in the Control and Treated Groups Reported to Have Had Various Conditions in Their Medical History

Type of Condition[a]	Number of Cases with —						Percentage of Cases[d] with —			
	Sufficient History to Indicate Presence or Absence of Condition[b]		Condition Present[c]		Condition Absent		Condition Present[b]		Condition Absent[b]	
	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group
A *Pre-existing Heart Disease and Consequences Thereof*										
1 Coronary heart disease:										
a. Anginal syndrome	428	570	223	285	205	285	52.1	50.0	47.9	50 0
b Coronary artery disease .	406	547	205	264	201	283	50.5	48.3	49.5	51.7
c Previous myocardial infarction	412	550	99	123	313	427	24.0	22.4	76.0	77.6
2 Other cardiac history										
a Other heart disease	404	529	44	67	360	462	10 9	12.7	89.1	87.3
b Congestive heart failure	430	571	66	82	364	489	15.3	14.4	84.7	85.6
c Cardiac arrhythmia—auricular fibrillation	423	563	6	9	417	554	1.4	1.6	98.6	98.4
B. *Pre-existing Cardiovascular Disease and the Consequences Thereof:*										
1. Arteriosclerosis	401	546	209	246	192	300	52.1	45.1	47.9	54.9
2 Hypertension	377	516	148	221	229	295	39 3	42 8	60.7	57.2
3 Cerebrovascular accidents	434	581	16	23	418	558	3.7	4.0	96.3	96.0
4 Thrombophlebitis	428	567	7	18	421	549	1.6	3.2	98.4	96.8
5 Gangrene	433	584	3	4	430	580	.7	.7	99.3	99.3
C *Conditions Which May Have Altered the Response to Anticoagulants*										
1 Hepatic disease	423	565	11	18	412	547	2.6	3.2	97.4	96.8
2 Renal disease	386	530	23	42	363	488	6 0	7.9	94.0	92.1
3 Hemorrhagic tendencies	432	583	6	5	426	578	1.4	.9	98.6	99.1
D *Miscellaneous Diseases*										
1 Diabetes mellitus	435	579	51	62	384	517	11.7	10 7	88.3	89.3
2 Gallbladder (biliary) disease	423	573	33	34	390	539	7.8	5.9	92.2	94.1
3 Gout	428	573	2	2	426	571	.5	.3	99.5	99.7
4 Recent operations (within 2 months)	352	488	3	9	349	479	.9	1.8	99.1	98.2

[a, b, c, d] See corresponding footnotes of Table 13

Coronary Artery Disease

The second most common condition reported in the past medical history of these patients was "coronary artery disease." The attending physicians had been advised to state that coronary artery disease had

TABLE 13

MEDICAL HISTORY OF THE TOTAL SAMPLE: Number and Percentage of Cases in the Total Sample Reported to Have Had Various Conditions in Their Medical History

Type of Condition[a]	Number of Cases with—			Percentage of Cases[d] with—	
	Sufficient History to Indicate Presence or Absence of Condition[b]	Condition Present[c]	Condition Absent	Condition Present[b]	Condition Absent[b]
A. *Pre-existing Heart Disease and Consequences Thereof:*					
1. Coronary heart disease:					
a. Anginal syndrome	998	508	490	50.9	49.1
b. Coronary artery disease	953	469	484	49.2	50.8
c. Previous myocardial infarction	962	222	740	23.1	76.9
2. Other cardiac history:					
a. Other heart disease	933	111	822	11.9	88.1
b. Congestive heart failure	1001	148	853	14.8	85.2
c. Cardiac arrhythmia-auricular fibrillation	986	15	971	1.5	98.5
B. *Pre-existing Cardiovascular Disease and the Consequences Thereof:*					
1. *Arteriosclerosis*	947	455	492	48.0	52.0
2. Hypertension	893	369	524	41.3	58.7
3. Cerebrovascular accidents	1015	39	976	3.8	96.2
4. Thrombophlebitis	995	25	970	2.5	97.5
5. Gangrene	1017	7	1010	.7	99.3
C. *Conditions Which May Have Altered the Response to Anticoagulants:*					
1. Hepatic disease	988	29	959	2.9	97.1
2. Renal disease	916	65	851	7.1	92.9
3. Hemorrhagic tendencies	1015	11	1004	1.1	98.9
D. *Miscellaneous Diseases:*					
1. Diabetes mellitus	1014	113	901	11.1	88.9
2. Gallbladder (biliary) disease	996	67	929	6.7	93.3
3. Gout	1001	4	997	.4	99.6
4. Recent operations (within 2 months)	840	12	828	1.4	98.6

[a] In addition to those conditions listed, some other pathological condition was specifically reported for 215 of the total of 1031 cases.

[b] Those for whom the history record submitted was insufficient to make possible a statement that a condition was or was not present are omitted from all computations of percentages. The number of such cases can be computed by subtracting the number reported below from 1031, the total number of cases in the sample.

[c] Forty-nine per cent of the entries for conditions present were supported by at least minimal explanatory notes. Doubt was expressed in about .5 per cent of the conditions tabulated as present.

[d] Based on number of cases with sufficient history to indicate presence of absence of condition.

On this basis, among the 951 patients with a satisfactory record, 63 per cent had characteristic history, or electrocardiographic evidence of previous clinical coronary artery disease.

Similar data by age are presented for the total sample in Table 15, and for the control and treated groups in Table 16 and Appendix F, Table 5 Both are demonstrated graphically in Figure 10. Although the percentage of patients fifty years and older who have evidence of previous coronary artery disease is definitely greater than the percentage of such patients younger than fifty years, *the relatively high incidence of pre-existing coronary artery disease in the younger patients is striking.* Fifteen, or 58 per cent of the 26 patients under 40 years of age had clinical evidence of previous coronary disease. This is compatible with the findings of Yater et al.[365] in their study of young men that all hearts at necropsy showed advanced arteriosclerosis of the coronary arteries and that the lesions in the coronary arteries in young men are similar to those seen in cases of coronary artery sclerosis in patients over 40, although such lesions are found to be more advanced in age as the men advance in years.

Previous Myocardial Infarction

The records of 962 patients in this series contained information regarding the occurrence or absence of myocardial infarctions prior to the attack under observation. Among these patients, 77 per cent had not experienced a previous infarction as far as could be determined; 23 per cent had experienced one or more previous infarctions; 4 per cent, two or more previous infarctions; and 0.5 per cent, three previous infarctions. These figures greatly understate the true prevalence of healed infarctions as will be demonstrated in the autopsy analysis (see pp. 445-446). The number and percentage of patients with a known record in the total sample and in the control and treated groups reported to have had one or more previous infarctions is summarized in Table 17 and demonstrated graphically in Figure 11. Differences between treatment groups were again minor and not statistically significant.

TABLE 16

PREVIOUS CORONARY ARTERY DISEASE, BY TREATMENT GROUPS: Percentage of Cases in the Total Sample and in the Control and Treated Groups with Any Clinical Evidence of Previous Coronary Artery Disease, by Age

Treatment Group	Percentage of Cases[a] with Any Clinical Evidence of Previous Coronary Artery Disease[b]							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
Total sample	63	*58*	52	63	69	66	*65*	—[c]
Control group	66	—[c]	49	70	69	64	—[c]	—[c]
Treated group	62	*47*	55	59	69	68	*64*	—[c]
	Number of Cases with Report on Previous Coronary Artery Disease							
Total sample	951	26	155	351	276	124	17	2
Control group	408	9	69	144	123	59	4	—
Treated group	543	17	86	207	153	65	13	2

Note *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable*

[a] Based on totals that exclude patients with an indeterminate history.

[b] See footnote a, Table 15

[c] Not computed since there were less than 10 cases in the sample.

existed clinically prior to the current attack of myocardial infarction only if the patient gave a history of pain which strongly suggested to the questioner previous attacks of angina pectoris or of myocardial infarction, or if electrocardiographic changes at the time of hospital entry supported such a statement. A past history of coronary artery disease was not reported solely because the patient exhibited advanced generalized arteriosclerosis or advanced age alone.

Among the 953 patients with actual reports on this condition, there had been previous evidence of coronary artery disease in about half (49 per cent). Differences by treatment groups were minor, the corresponding percentage for the control group being 50 per cent and for the treated group, 48 per cent.

In the hope of attaining a more complete estimate of the total incidence of pre-existing coronary artery disease among the patients in this study, further analysis was made. For this purpose, the minimum evidence required for any given case was a positive history of any one or more of the following (as previously defined): (1) coronary artery disease, (2) anginal syndrome, (3) previous myocardial infarction, or (4) electrocardiographic evidence of a previous infarction at the onset of the present attack.

TABLE 15

PREVIOUS CORONARY ARTERY DISEASE IN THE TOTAL SAMPLE: Number and Percentage of Cases in the Total Sample with Any Clinical Evidence of Previous Coronary Artery Disease, by Age

Previous Coronary Disease (Any Clinical Evidence of)[a]	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
	Number of Cases							
Present . . .	603	15	81	222	190	82	11	2
Not present . .	348	11	74	129	86	42	6	—
Indeterminate . . .	80	—	11	19	29	18	2	1
Total cases.	1031	26	166	370	305	142	19	3
Total with report (excluding indeterminate) . .	951	26	155	351	276	124	17	2
	Percentage of Cases[b]							
Present.	63	*58*	52	63	69	66	*65*	—[c]
Not present	37	*42*	48	37	31	34	*35*	—[c]
Total with report (excluding indeterminate) . .	100	*100*	100	100	100	100	*100*	—[c]

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Clinical evidence of coronary disease was defined for this tabulation as at least a report of "coronary disease" or "anginal syndrome," or a previous *infarction in the medical history*, or EKG evidence of a previous infarction

[b] Based on total cases with a report on previous coronary artery disease (i.e., excluding indeterminate).

[c] Not computed since there were less than 10 cases in the sample

Heart Disease Other than Coronary Artery Disease

Twelve per cent of the 933 cases for whom some statement was made on this point gave a history indicating the previous occurrence of heart disease other than coronary artery disease. "Other heart disease" in this study included etiological diagnoses such as arteriosclerotic, hypertensive, rheumatic and luetic heart disease, beri-beri heart, and subacute bacterial endocarditis; anatomical diagnoses such as valvular heart disease; and arrhythmias, such as tachycardias and fibrillation. Differences by treatment groups were inconsequential.

TABLE 17

PREVIOUS MYOCARDIAL INFARCTIONS: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Reported to Have Had One or More Myocardial [illegible]

	Number of Cases		
No previous infarction	740	313	427
One or more previous infarctions	222	99	123
Two or more previous infarctions	40	17	23
Three previous infarctions	5	1	4
Number of previous infarctions unknown	69	30	39
Total cases with report on number of previous infarctions[b]	962	412	550
Total, all cases	1031	442	589
	Percentage of Cases[c]		
No previous infarction	76 9	76 0	77.6
One or more previous infarctions	23 1	24 0	22.4
Two or more previous infarctions	4 2	4.1	4 2
Three previous infarctions	5	2	.7

[a] Of the previous infarctions reported, some doubt was expressed regarding [illegible] counted as having had none

[b] Number of cases with two or more, or three previous infarctions is not added into this total since these cases are represented by "one or more previous infarctions"

[c] Based on total cases for whom the number of previous infarctions was known.

Unfortunately, a previous history of other heart disease was indicated, but no description or explanation of the nature of the preexisting heart disease was given in many instances. Thus these data are of little value as an indication of the prevalence of associated cardiac conditions.

Congestive Heart Failure

Fifteen per cent of the 1001 patients reporting on this condition reported a positive history of congestive heart failure. There was little difference by treatment groups in this condition, corresponding percentages for the control and treated groups being 15 and 14 per cent respectively. The relation of this condition to the development of congestive heart failure at the time of the attack is reported on page 131.

Auricular Fibrillation

Among the 986 patients with a known history, 15, or 1.5 per cent, had experienced auricular fibrillation, the most common of the serious arrhythmias. Corresponding percentages for the control and treated groups were 1.4 and 1.6 per cent respectively. No inquiry was made regarding the other arrhythmias

Pre-existing Cardiovascular Diseases and the Consequences Thereof

Arteriosclerosis

The original instructions to the participating hospitals suggested that a history of arteriosclerosis be reported only when it included a symptom referable to this disease (e g., intermittent claudication), supported by signs of arteriosclerosis in the retinal and

It is interesting to note in passing that those who had had one or more previous infarctions were only about a year older on the average than those with no previous infarctions, the average age of the two groups being 60 and 59 years respectively. The difference seems less than one would expect from the typical interval between infarctions. One can surmise that the average age for persons with multiple infarctions is lowered by the heavy losses through death from the first infarction at the higher age levels. Whether the group with multiple infarctions is further characterized by unusually premature arteriosclerosis is not known.

In Table 18, the percentage of cases having no previous infarctions and those having one or more previous infarctions in this series are compared with several series from the literature. Master, Dack and Jaffe[123] found that the percentage of patients experiencing first, second and third attacks of coronary occlusion with myocardial infarction during each decade of adult life was approximately the same. These authors concluded that young and old persons were equally susceptible to subsequent attacks of coronary occlusion following an initial attack. One-third of all of their patients under seventy years had experienced at least one attack previous to that observed in their study. However, the mortality rate from acute coronary occlusion increased with each attack and with increasing age in each attack group. Doscher and Poindexter[52] found in their own material and in their review of the literature that the mortality rate from acute coronary occlusion increased with each major infarction.

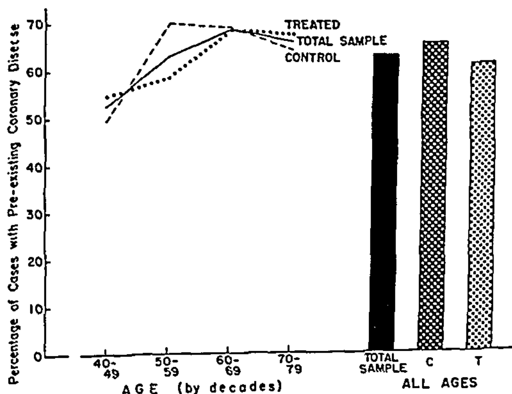


Figure 10. PRE-EXISTING CORONARY DISEASE: Percentage of cases in the total sample and in the control and treated groups with some clinical evidence of pre-existing coronary disease, by age.

Heart Disease Other than Coronary Artery Disease

Twelve per cent of the 933 cases for whom some statement was made on this point gave a history indicating the previous occurrence of heart disease other than coronary artery disease. "Other heart disease" in this study included etiological diagnoses such as arteriosclerotic, hypertensive, rheumatic and luetic heart disease, beri-beri heart, and subacute bacterial endocarditis; anatomical diagnoses such as valvular heart disease; and arrhythmias, such as tachycardias and fibrillation. Differences by treatment groups were inconsequential.

Unfortunately, a previous history of other heart disease was indicated, but no description or explanation of the nature of the pre-existing heart disease was given in many instances. Thus these data are of little value as an indication of the prevalence of associated cardiac conditions.

TABLE 17

PREVIOUS MYOCARDIAL INFARCTIONS: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Reported to Have Had One or More Myocardial Infarctions Prior to the Attack Studied

Number of Previous Myocardial Infarctions[a]	Total Sample	Control Group	Treated Group
	Number of Cases		
No previous infarction	740	313	427
One or more previous infarctions	222	99	123
Two or more previous infarctions	40	17	23
Three previous infarctions	5	1	4
Number of previous infarctions unknown	69	30	39
Total cases with report on number of previous infarctions[b]	962	412	550
Total, all cases	1031	442	589
	Percentage of Cases[c]		
No previous infarction	76 9	76.0	77.6
One or more previous infarctions	23.1	24 0	22.4
Two or more previous infarctions	4.2	4.1	4.2
Three previous infarctions	.5	2	.7

[a] Of the previous infarctions reported, some doubt was expressed regarding 15 3 per cent To simplify tabulation, these were counted as definite Cases reported as probably having had no previous infarctions were counted as having had none

[b] Number of cases with two or more, or three previous infarctions is not added into this total since these cases are represented by "one or more previous infarctions"

[c] Based on total cases for whom the number of previous infarctions was known

Congestive Heart Failure

Fifteen per cent of the 1001 patients reporting on this condition reported a positive history of congestive heart failure. There was little difference by treatment groups in this condition, corresponding percentages for the control and treated groups being 15 and 14 per cent respectively. The relation of this condition to the development of congestive heart failure at the time of the attack is reported on page 131.

Auricular Fibrillation

Among the 986 patients with a known history, 15, or 1.5 per cent, had experienced auricular fibrillation, the most common of the serious arrhythmias. Corresponding percentages for the control and treated groups were 1.4 and 1.6 per cent respectively. No inquiry was made regarding the other arrhythmias.

Pre-existing Cardiovascular Diseases and the Consequences Thereof

Arteriosclerosis

The original instructions to the participating hospitals suggested that a history of arteriosclerosis be reported only when it included a symptom referable to this disease (e.g., intermittent claudication), supported by signs of arteriosclerosis in the retinal and

peripheral vessels. On this basis, 48 per cent of the patients in the total sample for whom this information was recorded showed systemic arteriosclerosis. There was some difference by treatment groups, 52 per cent of the control group and 45 per cent of the treated group showing this condition. While this difference is of borderline significance statistically, its meaning is not clear. In view of the large margin of error in the evaluation of this condition, it is doubtful that the apparent difference is of significance for the present study.

It is of interest that among the patients with known histories, anginal syndrome was reported for 51 per cent, coronary artery disease for 49 per cent and arteriosclerosis for 48 per cent, all closely similar proportions. That this similarity in percentages is significant is again doubtful because the cases with a positive history of each of these conditions are not identical and because errors in obtaining the past medical history must be expected. In addition, these percentages must be presumed to be understatements since the incidence of coronary arteriosclerosis and of systemic arteriosclerosis clinically is usually far less than that demonstrated at postmortem examination. Even when a special effort is made to demonstrate the presence of systemic arteriosclerosis, as by radiographic studies of the heart, the aorta and the peripheral vessels, only in the instance of relatively advanced arteriosclerosis is it possible to demonstrate conclusively the presence of arteriosclerotic lesions in a high percentage of cases.

Positive evidence of arteriosclerosis in any single vascular bed is commonly interpreted as evidence of a similar degenerative process throughout the vascular system, but it is noteworthy that manifestations of this process are characteristically patchy in their distribution. For example, Yater et al.[305] in the study of coronary artery disease in men under the age of forty years, found

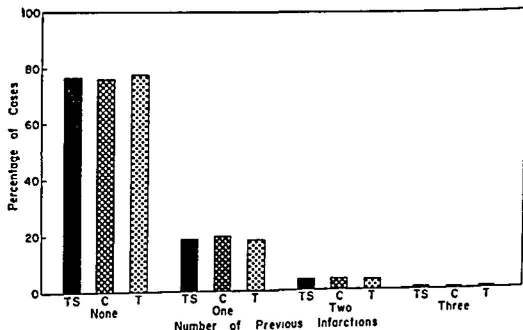


Figure 11. PREVIOUS MYOCARDIAL INFARCTIONS: Percentage of cases in the total sample and in the control and treated groups reported to have had one, two, or three previous myocardial infarctions or no myocardial infarctions prior to the present illness.

that whereas each of the 450 hearts examined at autopsy had advanced arteriosclerosis of the coronary arteries, only 191, or 42 per cent of the patients had some atherosclerosis of the aorta. Indeed, in 103 of these patients, the amount of atherosclerosis of the aorta was slight or moderate in comparison to the degree of coronary sclerosis. The only organs in which there were noteworthy arteriosclerotic lesions were the kidney, the brain and the adrenal glands and in these organs, the occurrence of important arteriosclerosis was numerically insignificant. Analysis of the autopsy data from the present study also revealed a similar unevenness in the degree of arteriosclerosis (see pp. 442–444).

Hypertension

Because of the wide interest in the relation of hypertension to myocardial infarction, the reports on pre-existing hypertension were tabulated in detail. Eighty-seven per cent of the replies included a "yes" or "no" statement regarding a history of this condition. Of those with a definite report in the total sample, 41 per cent were classed as having shown previous hypertension. Corresponding figures for the control and treated groups were 39 and 43 per cent respectively, a difference that may well be due to chance. These percentages are based on the categorical "yes" or "no" replies.

In many instances patients were able to quote, in addition, their usual systolic blood pressure prior to the present illness and, in some instances, also their diastolic pressure. In some cases hospital or physicians' records containing previous observations of the blood pressure were available so that specific blood pressure readings were quoted from them. These more specific reports were utilized in a second tabulation of antecedent hypertension. The hypertensive group was defined to include: (1) all cases with a systolic blood pressure of 150 millimeters or more, provided that diastolic blood pressure was at least 100 millimeters, or else unreported, (2) all cases with a systolic pressure below 150 millimeters, but with a diastolic pressure of 100 millimeters or more, (3) all cases with a diastolic pressure under 100 millimeters, but with a usual systolic blood pres[illegible] all [illegible] with[illegible] specific blood pressure readings. The normotensive group includes all cases whose usual blood pressure was reported and who were not hypertensive as defined in the preceding sentence. The information so obtained is tabulated by age for the entire sample in Table 19 and shown graphically in Figure 12. Among the 678 patients in the total sample whose usual blood pressures prior to the current illness

TABLE 18

PREVIOUS MYOCARDIAL [illegible]

Cases Having No Prev[illegible]

Se[illegible]

Number of Previous Myocardial I[illegible]	This Series	Willius[a]	Mintz & Katz[a]	Master, Dack & Jaffe[b] [a]	Doscher & Poindexter[a]
No previous infarction	76 9	80.3	92.5	59.4	86.5
One or more previous infarctions	23 1	19.7	7.5	33.0	13.5
Two or more previous infarctions	4 2	2.7	Patients having more than two attacks excluded from series	7.4	1.4
Three previous infarctions	.5	.5		.8	—

[a] For number of cases in these series, see Table 7.

[b] Percentages based on total sample, for 0 8 per cent of which the number of infarctions was not known.

were reported, 45 per cent were hypertensive. In spite of the smaller base, this figure is closely similar to that based on the categorical replies regarding previous hypertension. Differences by treatment groups can be deduced from Table 20 and Appendix F, Table 5. For the total groups (all ages), differences are minor and not statistically significant.

The relation of hypertension to coronary artery sclerosis and to acute coronary occlusion has attracted the attention of many observers. The incidence of hypertension in reported series of patients suffering coronary occlusion has varied widely, as is demonstrated in Table 21.

It has hitherto been generally agreed that hypertension and coronary artery disease

TABLE 19

USUAL PREVIOUS BLOOD PRESSURES FOR THE TOTAL SAMPLE: Number and Percentage of Cases in the Total Sample Reported to Have Had Usual Blood Pressures in the Hypertensive Range Prior to the Current Attack of Myocardial Infarction

Usual Previous Blood Pressure	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
	Number of Cases							
Normal or below[a]	372	14	66	136	100	48	7	1
Hypertensive[b]	306	3	40	105	105	44	8	1
No report	353	9	60	129	100	50	4	1
Total number of cases	1031	26	166	370	305	142	19	3
Total cases with usual previous blood pressure reported	678	17	106	241	205	92	15	2
	Percentage of Cases[c]							
Normal or below[a]	55	*82*	62	56	49	52	*47*	—[d]
Hypertensive[b]	45	*18*	38	44	51	48	*53*	—[d]
Total cases with usual previous blood pressure reported	100	*100*	100	100	100	100	*100*	—[d]

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] This group includes all cases with usual blood pressure reported who were not hypertensive as defined in footnote b.

[b] Classification based on usual blood pressure report with result that counts differ from those given for hypertension in Table 13 The hypertensive group was defined to include all cases with a systolic pressure of 150 millimeters or more provided the diastolic pressure was at least 100 or unreported, plus all cases with a systolic pressure below 150 but with a diastolic of 100 or more, plus all cases reported simply "hypertensive," or "high" (in blood pressure) without a specific reading, plus those with a [illegible] Unfortunately only 61 per [illegible] figure.

[c] Percentages based on cases with the usual blood pressure rep[illegible]

[d] Not computed since there were less than 10 cases in the group.

PREVIOUS HYPERTENSION

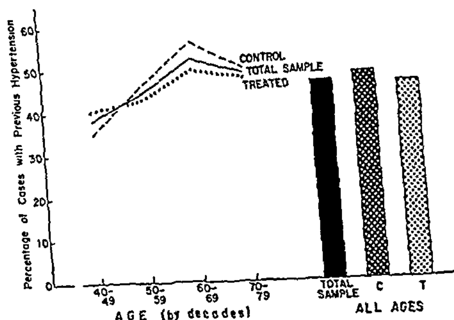


Figure 12. PREVIOUS HYPERTENSION: Percentage of cases in the total sample and in the control and treated groups reported to have had hypertension prior to the present illness, by age.

TABLE 20

USUAL PREVIOUS BLOOD PRESSURES FOR THE CONTROL AND TREATED GROUPS: Percentage of Cases in the Control and Treated Groups Reported to Have Had Blood Pressures in the Hypertensive Range Prior to the Attack of Myocardial Infarction

Treatment Group	Percentage of Cases[a] Reporting Usual Previous Blood Pressures in the Hypertensive Range[b]							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
Control group	47	—[c]	35	46	55	49	—[c]	—
Treated group	44	*10*	40	42	49	47	*58*	—[c]
	Number of Cases with Usual Previous Blood Pressure Report							
Control group	282	7	46	99	80	47	3	—
Treated group	396	10	60	142	125	45	12	2

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Percentages based on cases with the usual blood pressure reported.

[b] For definition of blood pressures considered in hypertensive range see footnotes a and b of Table 19.

[c] Not computed since there were less than 10 cases in the sample.

TABLE 21

PREVIOUS HYPERTENSION AS REPORTED IN OTHER SERIES: Incidence of Previous Hypertension among Patients Suffering Acute Coronary Occlusion as Reported in the Literature

Author(s)	Number of Patients in Series	Minimum Criteria for Hypertension	Percentage of Patients with Pre-existing Hypertension	Influence of Age and Other Comments
Data Obtained by Direct Observation				
Levine and Brown[118]	145	160/100	40.0	68.3% of patients were between 50 & 69 years Other patients had clinical evidence of pre-existing hypertension.
Conner & Holt[41]	274	—	33.9	Highest incidence in age group 56 to 60 years.
Allan[3]	140	—	73.0	—
Palmer[174]	212	—	73.0	37% in patients under 50, 78–84% in patients 50 to 80 years.
Master, Dack & Jaffe[140]	500	150/90	62.4	Frequency of hypertension rose directly with age. Hypertension in men, 25–34 years, 28%; 75 years and over, 80%.
Master *et al.*[143]	538	—	69.0	Increased incidence with age. Hypertension more common with multiple attacks.
Gross and Engelberg[78]	100	—	90 0	—
Rathe[188]	274	—	63.0	—
Chambers[43]	100	—	74.0	—
Doscher & Poindexter[52]	414	Diastolic pressure 100 or more	36.7	Patients with HBP which fell to normal excluded.
Mintz and Katz[152]	572	Diastolic pressure over 90	35.9	Low incidence in younger age groups; in older age groups, incidence, especially in women, increased with age. In women 49.4%; in men 29 7%
Data Obtained by Review of Literature				
Allan[3]	Several series	—	25.0–59.0	—
Doscher & Poindexter[52]	4035	140/90 to 160/110	46.0	In 1745 cases from literature, including authors' own, hypertension occurred in: 37.2% of 1334 males, 63 0% of 420 females
Mintz and Katz[152]	—	—	28.0–69.0	—

are intimately related. Levine and Brown[111] stated that "A pre-existing hypertension is probably the most common etiological factor in the development of myocardial infarction in the majority of cases." Master, Dack and Jaffe[149] concluded that "hypertension is an etiological factor in coronary occlusion, for its incidence in our series was definitely greater than that calculated for the general population. Furthermore, the ratio of attacks per unit of the hypertensive male population was five to eight times as great as that for patients with normal blood pressure, although both ratios increased with age in the same proportion. Hypertension accelerates the aging process." Yater et al.[165] concluded that "It appears that there is some relationship between coronary artery disease and hypertension which increases with age. It may be that there is a hereditary predisposition to the two diseases or that there is a common etiological factor. Another possibility is that reduction in the coronary blood flow resulting from disease of the coronary arteries may cause hypertension as a compensatory mechanism to increase the head of pressure in the coronary arterial tree."

Subdivision of the hypertensive findings by sex for the present study revealed that *pre-existing hypertension was almost twice as frequent in the histories of the women in this series as in those for men.* Sixty-four per cent of the women with a known history in this regard, but only 38 per cent of the men had shown hypertension prior to the attack studied. This difference is highly significant statistically and remains unchanged when standardized for age.*

This sex difference in pre-existing hypertension among persons suffering coronary occlusion has been repeatedly substantiated by other observers, although actual contrasts reported differ from study to study. Master, Dack and Jaffe[138] found that 56.5 per cent of their male patients and 80 per cent of their female patients were hypertensive. Mintz and Katz[133] observed that 29.7 per cent of their men and 49.4 per cent of their women were hypertensive. Doscher and Poindexter[51] reported that in a total of 1745 cases from their own series and from collected series in which the sex distribution was noted, 37.2 per cent of the males and 63.0 per cent of the females were hypertensive. They suggested that the discrepancy between the frequency of hypertension in the literature is explained in part by the various standards used for the definition of hypertension and in part by difference in the sex ratios in the various series.

A more recent [illegible] relation of blood pressure to coronary occlusion. This study was undertaken to establish limits of normal blood pressure in relation to age and sex. The limits of normal blood pressure, as determined by the method utilized, were found to be definitely higher than the commonly accepted ones, and to vary with age and sex. When the new definitions of "hypertension" according to age and sex were applied to a series of 554 consecutive patients with coronary occlusion under the age of 65, 35 per cent of those with a known record (454 cases) were found to be hypertensive. The frequency of hypertension was higher among the women (71 per cent) than among the men (27 per cent). In each age group (five-year periods between 35 and 64), the frequency of hypertension among the women was more than twice that among the men. Using the new limits for normotension, the incidence of hypertension remained fairly stationary, even though the actual blood pressure levels rose with increasing age. These authors concluded, therefore, that there was no close relationship between hypertension and coronary artery disease or coronary occlusion in males less than 65 years of age. Hypertension did appear, however, to have an important relationship with coronary occlusion in women.

* When rounded to the nearest whole percentage, the rates after age standardization were the same as those quoted above.

Subdivision of the hypertensive findings by age (see Table 19) revealed further a moderate upward trend with age in the percentage of cases with pre-existing hypertension, the peak period being in the seventh decade. The actual trends are shown graphically in Figure 12. Separate inspection of these trends for men and women revealed, however, that this upward trend was produced in part by the increasing proportion of women at the older age levels. When the age trends were studied separately for the two sexes, the women showed no upward age trend for hypertension[b] while the men showed only moderate increases, the percentages for consecutive decades beginning with ages under 50, 50–59, etc. being in sequence: 31, 39, 43, and 37 per cent. These trends, moreover, are based on a single standard for all ages. If the definition of normal had been varied according to the age and sex of the patient, as suggested by Master, Garfield and Walters,[141] even this small increase with age might have disappeared.

Other observers have also noted an increase with age in the proportion with hypertension when a single definition of this condition was used. Master, Dack and Jaffe,[138] using a single definition of hypertension, found that the frequency of hypertension rose directly with age, from an incidence of 36 per cent in the fourth decade to 74 per cent in the seventh decade. When the incidence of hypertension was calculated separately for each sex, these authors found that, while only 28 per cent of the males and 25 per cent of the females between the ages of 25 and 34 were hypertensive, 80 per cent of the males over 75 years and 90 to 100 per cent of the females over 45 years were hypertensive. Palmer[174] reported that 37 per cent of his patients under the age of 50 were hypertensive, but that 78 to 84 per cent of the patients between 50 and 80 years were hypertensive. Mintz and Katz[152] reported a low incidence of hypertension in their younger patients, but noted that among their older patients, especially among the women, the incidence of hypertension increased with age. Master et al.[142] observed the same increase in incidence of hypertension with age. Conner and Holt[45] observed that the highest incidence of hypertension occurred in patients between the ages of 56 and 60 years. On the basis of the findings of Master, Garfield and Walters,[141] it is apparent that increases in blood pressure with age are typical not only of coronary thrombosis cases but also of the general population.

Cerebrovascular Accidents

A history of a cerebrovascular accident was relatively uncommon. Thirty-nine patients, or 3.8 per cent of the 1015 with a known history, had experienced a cerebrovascular accident of one sort or another. The control and treated groups were approximately comparable in this respect, the percentages being 3.7 and 4.0 per cent respectively. Supplementary information furnished in many instances indicates that the accidents were not closely related in time to the attack of coronary thrombosis under study, all but one having occurred at least three months previously.

Thrombophlebitis

The incidence of thrombophlebitis was similarly low. Three per cent of the 995 for whom a statement was made were reported to have suffered an attack of thrombophlebitis in the past. A history of this condition was reported for 2 per cent of the control group and 3 per cent of the treated group. In two cases, this condition was reported present at the time of admission to the hospital and in the third, the patient had been hospitalized for thrombophlebitis until four days prior to the present attack. All these cases posed the diagnostic problem of distinguish-

[b] Consecutive decades beginning with ages under 50, 50–59, etc. showed the following percentages of the women with a history of hypertension: 64, 65, 63, and 64 per cent.

ing between a possible pulmonary embolus originating in the extremities and a myocardial infarction.

Gangrene

No association between gangrene and coronary thrombosis was apparent in the histories of these cases. Gangrene was reported in only 7 instances (0.7 per cent of the 1017 instances in which information on this point was obtained). Corresponding percentages for the control and the treated groups were the same as for the total sample, namely, 0.7 per cent. The interval between the gangrene and the present attack was at least a year in all cases with amplifying notes, except one. The exception was a case with diabetes who had had a toe amputation 12 days prior to the present attack.

Conditions Which May Alter the Response to Dicumarol

Renal Disease

Seven per cent of the 916 patients with a known history in this respect had a history of some renal or genito-urinary disease. The types listed were varied, the only apparent concentration being in renal lithiasis and nephritis of various types. Among patients for whom this information was given, 6 per cent of the control group and 8 per cent of the treated group had a history of renal or urinary tract disease. The difference is inconsequential.

Liver Disease

No association between coronary thrombosis and liver disease was apparent. [illegible]

[illegible] ...plementary information concerning the nature of the hepatic disorder showed jaundice and hepatomegaly of unspecified etiology to be the only types mentioned with any frequency. A history of liver disease was equally infrequent in both the control and treated groups, namely, 3 per cent of those with a known record in each group.

Hemorrhagic Tendencies

Relatively few patients reported a history of previous hemorrhage. Only 11 patients (1.1 per cent of the 1015 with a known history in this connection) were reported to have experienced hemorrhagic phenomena. Those mentioned included such common phenomena as epistaxis, hematuria, hematemesis, melena, and retinal bleeding. *No instance of true hemorrhagic diathesis was described in the cases included in this series. Apparently there was no difference of consequence in the susceptibility to bleeding in the two treatment groups prior to anticoagulant therapy* since hemorrhagic episodes were described as having occurred previously in 1.4 per cent of the control cases and 0.9 per cent of the treated cases with a known record. Thus, differences later observed in the incidence of bleeding during anticoagulant therapy may be presumed to be related to the therapy received.

Only one of the 5 cases in the treated group with a reported history of hemorrhagic tendencies actually bled during the period of observation and in this case, anticoagulants had been withheld entirely because of gross hematuria, bladder calculi, and a hernia repair prior to onset of the attack. In another case, anticoagulants were also withheld because of a history of hemorrhagic tendencies. None of the three treated group cases with a history of hemorrhagic tendencies who received anticoagulants developed bleeding. One of these was a case with a history of recurrent hematemesis, presumably from gastric ulcer. Because of this history, anticoagulants were withheld until the patient developed venous thromboses in both legs and a pulmonary embolus on the same day. Both heparin and dicumarol were started on the next day and were used for two days without hemorrhage but the patient died notwithstanding, the pulmonary infarction being a contributing cause. With less hesita-

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[b] Consecutive decades beginning with ages under 50, 50–59, etc. showed the following percentages of the women with a history of hypertension: 64, 65, 63, and 64 per cent.

tion with respect to the use of anticoagulants, this death might have been prevented.

Miscellaneous Conditions

Diabetes Mellitus

Eleven per cent of the 1014 cases with information on this point reported diabetes in their medical history. There was little difference between the control and treated groups in this respect, corresponding percentages being 12 and 11 per cent respectively (see Table 22, Figure 13, and Appendix F, Table 6).

These relatively high prevalence ratios were to be expected since coronary sclerosis is common in patients with diabetes mellitus. Nathanson[160] observed coronary sclerosis at autopsy in 41 of 100 cases of diabetes. Joslin[104] found that patients with diabetes mellitus of 5 or more years' duration almost always had coronary sclerosis. Many observers have commented upon the great frequency of myocardial infarction in patients with diabetes. According to the reports of Enklewitz,[54] Master, Dack and Jaffe,[115] Bean,[14] White and Bland[212] and Levine and Brown,[115] diabetes occurs in from 10 to 23.7 per cent of all persons suffering acute myocardial infarction. On the other hand, Saphir et al.[211] have presented evidence that myocardial infarction is not as frequent in patients with diabetes mellitus as would be inferred from the literature.

An excellent study of coronary artery disease in patients with diabetes mellitus as determined at autopsy has been reported by Root et al.[193]

In the present series, 24 per cent of the women with a known record as contrasted

TABLE 23

PREVALENC[illegible] ...ion, by Sex

Type of Count and Sex	This Series: As Obtained from Patients' Histories	This Series: As Diagnosed during Current Hospitalization	Master Dack & Jaffe[115]	Dorcher & Poindexter[48]	Collected from the Literature—Dorcher & Poindexter[48]	Mintz & Katz[136]
Number of cases						
Males	774[b]	789	—[a]	—[a]	890	392
Females	240[b]	242	—[a]	—[a]	327	180
Both sexes	1014[b]	1031	500	414	2389	572
Number of diabetics						
Males	55	50	—[a]	—[a]	74	36
Females	58	50	—[a]	—[a]	101	49
Both sexes	113	100	—[a]	32	265	85
Percentage of cases with diabetes:						
Males	7.1[c]	6.3	6.7	—[a]	8.3	9.2
Females	24.2[c]	20.7	26.0	—[a]	30.9	27.2
Both sexes	11.1[c]	9.7	11.2	7.9	11.1	16.2

[a] Not reported.
[b] Number of cases from whom history on this point was obtained.
[c] Based on number of cases for whom history on this point was obtained.

TABLE 22

PREVIOUS DIABETES, BY SEX: Percentage of Both Sexes and of Males and Females in the Total Sample and in the Control and Treated Groups Reporting Diabetes in Their Medical Histories

Basis of Diabetes Rate	Percentage of Cases[a] Reported to Have Had Diabetes Previously								
	Total Sample			Control Group			Treated Group		
	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females
Data as reported	11.1	7.1	24.2	11.7	8.5	23.2	10.7	6.0	24.8
Data standardized for age[b]	11.2	7.4	21.7	11.4	8.4	20.2	10.9	6.2	23.4
	Number of Cases with Report on History of Diabetes								
Total cases	1014	774	240	435	340	95	579	434	145

[a] Percentages based on the total number of cases whose history in regard to diabetes was known.

[b] These standardized percentages show what rates would have been if those for specific age groups in the present sample had prevailed but the proportion of cases in each age group were changed to those characteristic of the total sample, including those with an unknown record on this point.

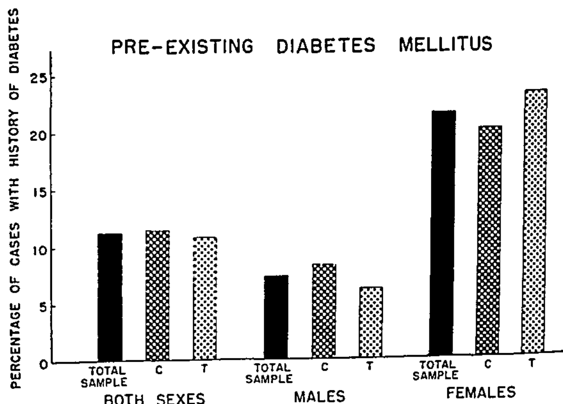


Figure 13. PRE-EXISTING DIABETES MELLITUS: Percentage of both sexes and of males and females in the total sample and in the control and treated groups reporting a history of diabetes mellitus (rates standardized for age).

first evident late in life, hastens coronary artery disease once it has developed.

There is a rather striking similarity in the incidence of diabetes mellitus among the males, among the females, and within the total sample in several series of cases of myocardial infarction reported in the litera- [illegible]

are presented along with similar data from this series.

The prevalence of diabetes mellitus in the general population of the United States is not known. Data such as that collected by the National Health Survey[274] are obviously an *understatement*, to what degree it is not possible to state. A more inclusive survey of a total population group, though one restricted to a very limited area, was that conducted in Oxford, Massachusetts, by the United States Public Health Service.[244] With full realization of the deficiencies of the data collected in these two surveys, the rates at which diabetes mellitus was observed in these two populations are compared by sex groups with the rates of diabetes mellitus observed in the current series, both on the basis of the histories reported and the findings during hospitalization, in Table 24 and Figure 14. *It is clear at a glance that the prevalence of diabetes among these coronary thrombosis cases was very much in excess of that in the general population of the same age and sex.*

Gallbladder Disease

Seven per cent of the 996 cases with reports in this respect were known to have experienced some biliary tract disorder, the most common type being cholecystitis. Differences between the control and treated groups were minor (control group, 8 per cent, *vs.* treated group, 6 per cent). No association with coronary thrombosis was apparent.

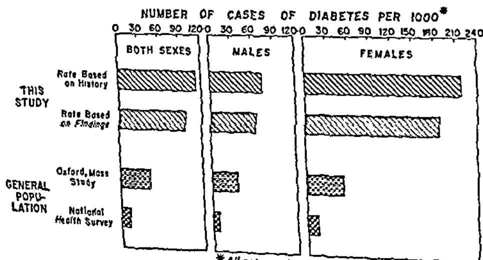


Figure 14. PREVALENCE OF DIABETES IN SERIES AND IN GENERAL POPULATION: Number of cases of diabetes mellitus per 1000 persons in the present series and in two general population surveys, by sex.

TABLE 24

PREVALENCE OF DIABETES MELLITUS IN THIS SAMPLE AND IN THE TOTAL POPULATION: Number of Cases of Diabetes Mellitus per Thousand Persons in the Total Sample and among the General Population as Reported in Two Population Surveys, by Sex

Survey	Number of Cases of Diabetes per 1000 Persons					
	Reported Rate for All Age Groups Combined			Rate Adjusted to Age Composition of the Total Sample (Both Sexes) in the Present Study[a]		
	Both Sexes	Males	Females	Both Sexes	Males	Females
Coronary Thrombosis Cases (data from this study):						
Rates based on cases reported to have a history of diabetes[b]	111	71	242	112	74	217
Rates based on cases with findings of symptoms of diabetes during hospitalization for coronary attack studied.	97	63	207	97	65	187
General Population:						
Oxford, Mass., study, 1946–47[c]........	17	17	18	45.4	38.1	53.2
National Health Survey, 1935–36[d]......	4.3[e]	3.3[e]	5.4[e]	12.6	9.3	15 5

[a] Adjustments were made with the standardization procedure explained in footnote b, Table 22

[b] Rates are based on totals that exclude cases with an indeterminate history with respect to diabetes (see Table 23).

[c] A systematic community study of the prevalence of the disease which included tests for the disease among the majority of the population (3,516 persons) See Wilkerson and Krall [344]

[d] Spiegelman and Marks [324]

[e] Rates adjusted to the age composition of the Oxford study and furnished in personal letter from Dr. Louis I. Dublin of the Metropolitan Life Insurance Company. Rate for males without this adjustment is 2.7 and for females, 4.5.

with only 7 per cent of the men had a history of diabetes (see Table 22 and Figure 13). Master, Dack and Jaffe[185] found among their patients with coronary occlusion that diabetes is frequent in women 50 years of age and older, but that it is uncommon in men until the age of 70 is reached. These authors concluded that diabetes plays no role in the development of myocardial infarction in men at any age, or in young women, but that it does play a definite role in the occurrence of myocardial infarction in women older than 50 years. They found that the clinical course following coronary occlusion was more severe and the degree of coronary sclerosis present more advanced in diabetic women older than 50 years than in nondiabetic women of the same age observed by them.

Analysis of the age of cases with a history of diabetes in the present series showed cases with such a history to have a slightly higher average age than those without such a history.[a] While this observation would seem to contradict the belief that diabetes hastens coronary artery disease, the present finding probably has no significance other than as an indication that diabetes is a disease of older persons. In spite of these findings, it may well be that diabetes, even when it is

[a] Among cases with a history of diabetes, the average age was 63 0 years for both sexes, 60 8 for males, and 65 0 for females. For cases with no history of diabetes, the average age was 58 6 for both sexes, 57.4 for males, and 63.2 for females.

toms of their illness to those of other comparable studies and to the experience of physicians regarding the typical characteristics of the condition. Additional assurance is afforded by the quality of the medical judgment exercised by physicians in the cooperating hospitals and the care used in excluding cases with a doubtful diagnosis.

This favorable evaluation is subject to several qualifications that are important for interpretation. In the first place, it is obvious, for example, that the restriction of the *sample* to hospitalized cases, cases surviving the first 24 hours of hospitalization, and cases where the diagnosis was not in doubt, had important effects on the findings, for *these restrictions operated to exclude both the very mild cases and those that were fatal either immediately or very shortly after the attack.* Care should be [illegible] for *had such cases been included, many resulting percentages would have been grossly different, as for example, the death rates.* This qualification should not be interpreted to mean that the study does not throw light on the results of anticoagulant therapy in mild or moderately ill or good risk patients. The sample does include a substantial number of such cases, and rates for deaths, thromboembolic complications and hemorrhages were separately computed for such cases. These rates give an indication of the potentialities of anticoagulant therapy with cases of the type sometimes not hospitalized. The *other* omissions, those of cases dying within 24 hours of hospitalization and cases not surviving long enough to be hospitalized, do not prevent the achievement of the basic purpose of the study since such patients can seldom be helped by anticoagulant therapy in any case.

The second qualification arises from the manner in which the sample is known to have been selected. Data as to the cases studied indicate that the sample covers a population group that should be described as predominantly white, urban, and from the lower income groups. Representation of the southern areas was also proportionately low. Whether these characteristics of the sample are of any significance for a study of coronary thrombosis patients is not known.

These qualifications regarding the representativeness of the total sample must not be allowed to confuse the issue of the comparability of the control and treated groups. Within the total sample, assignment of cases to the control and treated groups was intended to be random, the odd- and even-day criteria for assignment being designed to produce this result. While the resulting proportion of odd-day cases exceeded reasonable chance limits, with very minor exceptions, this excess does not appear to have been produced by selective factors that adversely affected comparability for the purposes for which the study was designed. At each step in the analysis, a careful attempt has been made to evaluate statistically the extent to which this essential comparability was actually achieved. If no bias correlated with the results of treatment entered into the assignment of cases to anticoagulant therapy, the two groups would not, except in rare instances, differ from each other in *relevant characteristics* beyond the limits expected on a chance basis, *except in regard* to traits affected by anticoagulant treatment.

Actual comparisons have been scattered throughout the text. Twenty-two of the comparisons made with respect to the characteristics of the patients prior to the attack were subjected to tests of statistical significance. These were as follows:

1. Distribution of cases by age (for distributions, see Table 8)
2. Geographic distribution of cases (measured by distribution by hospitals as shown in Table 4, Chapter III)
3. Percentage of women (22 per cent, control, *vs.* 25 per cent, treated)
4. Percentage within normal weight range (56 per cent, control, *vs.* 58 per cent, treated)

Gout

It is of considerable interest that, of the 1001 patients reporting in respect to gout, only 4 patients, or 0.4 per cent of this number, were reported to have any knowledge of having suffered this disease. A relationship between gout and coronary artery disease has been commented upon by various clinical observers, but *our material suggests that any occurrence of the two conditions together is purely coincidental.*

TABLE 25

OPERATIONS PRECEDING THE ILLNESS: Details Reported Regarding Cases with a History of Operations within Two Months

Type of Operation	Time before Present Attack	Remarks
Control Group:		
Polypectomy, colon	44 days	—
Incision, abscess, infraorbital	28 days	same patient
Extirpation, lachrymal duct	8 days	same patient
Vein ligation	40 days	saphenous, bilateral
Treated Group:		
Prostatectomy, perineal	—	same patient
Urethroplasty	5 days	same patient
Ureterectomy, left	same day	for pyoureter
Resection, prostatic	27 days	transurethral
Exploration	9 days	perinephritic abscess
Ligation and stripping	same day	varicose veins, bilateral
Extraction, cataract	7 days	intracapsular
Amputation, right great toe	12 days	for diabetic gangrene
Cystoscopy	3 days	same patient
Hernia repair, right femoral	3 days	same patient
Removal, intervertebral disc	14 days	

Recent Operations

In a few instances, surgical operations had been performed on patients in this series shortly before the onset of the presenting attack of coronary occlusion. Twelve patients, or 1.4 per cent of the 840 with a report on this point, had experienced one or more surgical operations within 2 months prior to the onset of their coronary occlusion with myocardial infarction. The operations involved are enumerated in Table 25. Among the control patients, 0.9 per cent were reported to have had a recent surgical operation; among the treated patients, 1.8 per cent were so reported. In two instances, the current attack of coronary occlusion occurred on the same day as a surgical procedure.

SUMMARY EVALUATION OF THE CHARACTERISTICS OF THE SAMPLE

A review of these specific characteristics of the sample indicates that in age, sex, and past medical history, these patients showed traits similar to those found in other studies of *hospitalized* patients with coronary thrombosis. Often the findings of this study assume approximately a median position in relation to corresponding measures from other studies. For other characteristics where comparative data were unavailable, serious biases were likewise not obvious. This similarity with other comparable findings is particularly gratifying since it was not administratively feasible to select for this study a truly random sample of all cases of coronary thrombosis with myocardial infarction in all hospitals in the country, for such a sampling would have required cooperative arrangements for both standardized treatment and reporting with most of the hospitals in the country. The major assurance of the representativeness of the total sample as a picture of *hospitalized* patients with coronary thrombosis thus lies in the similarity of the findings as to the types of patients included and the signs and symp-

ated with confidence but the differences are obviously of small magnitude and probably of little consequence in their effect. Thus it is clear that the balance of influences thus far reported was sufficiently close to avoid any obvious initial advantage to either group in the experiment. Moreover, in all but one of the above proportions tested for significance, the differences between the control and treated groups as finally constituted were found "not statistically significant."[4] In other words, the evidence regarding differences is insufficient to disprove, at the adopted level of significance, the hypothesis that the two groups were drawn from the same population. In the case of one exception, namely, the difference in respect to a history of arteriosclerosis, the difference was of borderline significance only. The greater difference in respect to a history of arteriosclerosis is probably meaningless since (1) a large margin of error in the clinical evaluation of this aspect of the history is to be expected and (2) occasional differences (i.e., about 1 in 20) can be expected to exceed the 5 per cent level of significance on a chance basis only. Therefore, the basic test of the effectiveness of anticoagulant therapy may be considered to have been made on control and treated groups that did not differ significantly in their basic composition as evaluated from data relative to the patients prior to their attack.

Similar comparisons of the two groups in regard to the nature of the onset and course of their illness are made in the following chapter. Some of these later comparisons throw further light on the nature of the sample studied and the comparability of the two groups.

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among those with this history in the control group since this reversal was felt to be due perhaps to underreporting of previous infarctions (see pp. 328-329).

[4] The tests of significance throughout the report are designed to minimize the chances of stating that a true difference existed when, in fact, there was no difference between the populations sampled. The procedures used also give the maximum protection against the opposite type of error (namely, that of stating that no significant difference exists, when, in fact, there is a true difference between the populations sampled) that is possible without altering the first objective. The actual chances of failing to detect a true difference vary according to the pooled level of the observed percentage for the total sample, the number of cases observed, and the amount of the true difference. For pooled percentages in the neighborhood of 15 per cent, the chances of failing to identify a true difference of as much as plus or minus 10 per cent between the two total treatment groups sampled by terming the results "borderline" [illegible] crease upward to a maximum of about one chance in five of failing to detect a true difference of this amount for proportions at the 50 per cent level for these same groups. On the other hand, the chances of detecting differences increase rapidly as the size of the true difference increases.

5. Percentage of cases with a history of of anginal syndrome (52 per cent, control, *vs.* 50 per cent, treated)
6. Percentage of cases with a reported history of coronary artery disease (50 per cent, control, *vs.* 48 per cent, treated)
7. Percentage of cases without clinical evidence of previous coronary disease (34 per cent, control, *vs.* 39 per cent, treated)
8. Percentage of cases with history of one or more previous infarctions (24 per cent, control, *vs.* 22 per cent, treated)
9. Percentage of cases with other types of previous heart disease (11 per cent, control, *vs.* 13 per cent, treated)
10. Percentage of cases with history of congestive heart failure (15 per cent, control, *vs.* 14 per cent, treated)
11. Percentage of cases with history of auricular fibrillation (1.4 per cent, control, *vs.* 1.6 per cent, treated)
12. Percentage of cases with a previous history of hypertension (39 per cent, control, *vs.* 43 per cent, treated)
13. Percentage of cases with usual blood pressure readings in the hypertensive range (47 per cent, control, *vs.* 44 per cent, treated)
14. Percentage of cases with a known history of arteriosclerosis (52 per cent, control, *vs.* 45 per cent, treated)
15. Percentage of cases having had one or more cerebrovascular accidents prior to the attack (3.7 per cent, control, *vs.* 4.0 per cent, treated)
16. Percentage of cases with a history of thrombophlebitis (1.6 per cent, control, *vs.* 3.2 per cent, treated)
17. Percentage of cases with previous renal disease (6 per cent, control, *vs.* 8 per cent, treated)
18. Percentage of cases with previous hepatic disease (2.6 per cent, control, *vs.* 3.2 per cent, treated)
19. Percentage of cases with history of hemorrhagic phenomena (1.4 per cent, control, *vs.* 0.9 per cent, treated)
20. Percentage of cases with a history of diabetes mellitus (12 per cent, control, *vs.* 11 per cent, treated)
21. Percentage of cases with a history of gallbladder disease (8 per cent, control, *vs.* 6 per cent, treated)
22. Percentage of cases with an operation within two months (0.9 per cent, control, *vs.* 1.8 per cent, treated)

It will be noted that the differences are consistently small in amount and that some are almost imperceptible. Moreover, their direction is mixed. Under these circumstances their net effect is difficult to evaluate. For 19 of these items, however, the probable direction of their influence on deaths, complications, or hemorrhages is fairly clear either from clinical experience or from data presented in subsequent chapters. Of these 19, the direction of 10 of the differences would be expected to favor the treated group and the direction of the other 9, to favor the control group.[d] The direction of the influence of the conditions covered by the remaining items, namely 2, 5, and 7,[e] cannot be evalu-

[d] Items 3, 9, 11, 12, 15, 16, 17, 18 and 22 are here counted favorable to the control group and items 1, 4, 6, 8, 10, 13, 14, 19, 20 and 21 are considered favorable to the treated group

[e] Although on first inspection, items 5 and 7 would appear to favor the treated group, Chapter XI reports that control group cases with a history of anginal syndrome and those with any clinical evidence of previous coronary disease showed a lower death rate than those without such histories, while those in the treated group with an anginal syndrome history showed essentially the same death rate as those without such a history. (See p. 328-329 for a discussion of these findings) In view of these findings, the direction of the effect of these items is questionable In addition, there is considerable duplication between items 5, 6, 7 and 8. For these reasons, items 5 and 7 are omitted from the evaluation of balance between the two groups (i e., considered neutral) Item 8 (previous infarctions) has been considered favorable to the treated group even though a similar reversal of expectation occurred in the percentage dying

TABLE 26

CIRCUMSTANCES OF ONSET: Circumstances or Events Which May Have Been Immediate, Provoking, or Precipitating Causes for Myocardial Infarction in Selected Cases in the Control and Treated Groups

Circumstances or Events Preceding Onset*	
Onset following effort, emotional disturbances, trauma	Onset following operation, medication, or medical procedure
While chopping wood.	Following giving of enema to patient.
While lifting lumber.	Followed by 6 days an urethroplasty performed to correct urinary incontinence which followed perineal prostatectomy.
While bowling	Followed by 12 days the amputation of the right great toe for diabetic gangrene
While watering lawn.	Followed by 7 days an intracapsular cataract extraction.
While mowing lawn.	On same day after patient was bronchoscoped twice for collapse of right lower lobe
During intercourse.	Patient was admitted with fracture of the neck of the left femur. An EKG taken one week later showed the patient to have a myocardial infarction which was believed to have occurred simultaneously with, or shortly after, the fracture
Several hours after anoxemia and exercise tolerance test.	Cerebral accident and myocardial infarction occurred during cholecystography performed with oral dye.
Policeman struck over precordium during struggle with inebriate. There was considerable *exertion* during the altercation. Symptoms appeared promptly after *blow* was struck.	Patient had been taking benzedrine for chronic fatigue for the preceding 6 months; medication had produced insomnia, nervousness and irritability.
Immediately after emotional upset (cause and nature unknown)	On same day as left ureterectomy (pyoureter).
	On same day as bilateral ligation and stripping—varicose veins.
	Following by 4 days a right femoral hernia repair and a cystoscopy.

* Each circumstance applies to one case only.

trauma may play a definite part in the development of coronary occlusion by thrombosis.[44, 68, 101, 210]

Instances of coronary occlusion with myocardial infarction which appeared to have been related to trauma, to exertion and to emotional disturbances occurred in this series. Other instances occurred during the postoperative period and immediately or shortly after various therapeutic and diagnostic procedures. It is doubtful that such relationships were recognized in all instances in which they occurred, or that all were reported. However, the instances that were reported were reviewed and the more unusual circumstances mentioned as related to the onset of the attack of acute myocardial infarction studied are listed in Table 26.

The *Site of the Initial Infarction as Diagnosed Clinically*

The site of the initial infarction occurring during the current illness was reported in each instance in which its location could be determined electrocardiographically. The criteria for the localization of infarctions varied somewhat among the participating hospitals, but was, in general, consistent with standards accepted generally. The hospitals were requested to include in the

CHAPTER V

The Course of the Present Illness: Part 1. Onset, Symptoms and Signs

THIS and the following chapter present a detailed analysis of the course of the illness for the patients in this series as revealed by the initial characteristics at onset and the symptoms, signs, syndromes, laboratory findings and miscellaneous complications. This analysis is designed to serve the following functions:

1. To provide a composite picture of the relative frequency of various signs and symptoms in hospitalized cases of myocardial infarction.

2. To give perspective regarding the present series by exploring similarities and differences between the frequency of symptoms in this and other series.

3. To check the comparability of the control and treated groups in respect to the characteristics of the illness prior to the administration of anticoagulants.

4. To evaluate, where possible, with the data at hand the extent to which the course of the illness was affected by anticoagulant therapy.

5. To observe the variations in symptomatology with age and the time after onset.

6. To summarize the signs and symptoms that foretell a poor prognosis.

This presentation is divided between two chapters, only the onset, symptoms and signs being treated in the present chapter. For better integration, the summary and conclusions regarding the course of the illness are reserved for the end of Chapter VI.

ONSET

Circumstances and Events Which May Have Precipitated or Provoked an Infarction

The occurrence of a myocardial infarction is not infrequently preceded by, or associated with, an event, or a set of specific circumstances which appears to be directly responsible for the acute episode.[22, 25, 28, 32, 127, 134, 136, 137, 139, 151, 157] A sequence of cause and effect is often readily accepted by the layman, but less readily, by the physician. As Boas[31] has pointed out, the extrinsic factors which most commonly appear to precipitate myocardial infarction are effort, emotion, cold, and overeating. To these must be added an infrequent but undoubted factor, trauma. It is the general opinion that except for direct trauma to the precordium these factors do not ordinarily precipitate myocardial infarction when the coronary arterial system is normal, but only when the coronary circulation has been impaired by sclerosis and the myocardium damaged by degenerative changes.

Myocardial infarction occurring during the postoperative period[27, 35, 147, 196] is readily explained in those instances where shock and/or hemorrhage have reduced the effective circulating blood volume and, consequently, the coronary blood flow. This is particularly important in patients whose coronary circulation has already been impaired by narrowing or occlusion of coronary vessels by sclerotic changes. Hypercoagulability of the blood following surgery or

septum. Thirty-seven per cent had a posterior, a posterolateral, or a posteroseptal infarction. Thirteen of these (1.3 per cent of the total sample) involved both the posterior wall and the septum. Fifteen cases (1.4 per cent) were reported to have had purely septal infarctions. The percentages of cases [illegible] showed no significant differences.

When the percentage of cases with recent infarctions in various locations in this series is compared with the location of infarctions in certain other series reported in the literature, as in Table 28, there is rather surprising agreement. One may conclude that, clinically, slightly more than 50 per cent of all infarctions are anterior, including anterolateral and anteroseptal. In those series in which the incidence of anterior infarctions is lower than this, the percentage of infarctions reported as "not localized" is relatively high. Posterior infarctions, including posterolateral and posteroseptal infarctions, may be said to occur in from 35 to 40 per cent of all cases. Again, lower percentages are reported only in those series in which a relatively high percentage of infarctions were not localized. There is a rather wide discrepancy in the reporting of lateral and septal infarctions and in those not localized, undoubtedly due in part to the differences in the criteria used for the identification of these locations.

Severity of Illness

The attending physicians who submitted the original reports were asked to estimate the severity of each patient's illness, first, in regard to the severity of onset, and second, in regard to the severity of the subsequent course under observation. It is obvious that such estimates, made by different observers or even by the same observer under a variety of circumstances, cannot be interpreted other than as general impressions which, in the aggregate, may indicate a trend.

An estimate of the severity of the onset and of the course of the illness was made for every case. The onset was reported to have been "mild" or "moderate" in 71 per cent of the total series, and "severe" in 29 per cent. The course of the illness was reported simi-

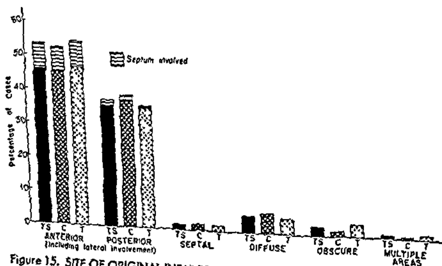


Figure 15. SITE OF ORIGINAL INFARCTION. Percentage of cases in the total sample and in the control and treated groups showing initial infarctions in various locations.

report of each case, not only a statement as to the location of the initial infarction, but also a detailed description of the electrocardiographic findings. When the interpretation of these findings in the Central Laboratory did not confirm the designated location, a request was made to the principal investigator to review the original case record and explain the discrepancy in interpretation.

The number and percentage of cases with *original infarctions in various locations* are summarized in Table 27 and portrayed graphically in Figure 15. In brief, multiple original infarctions, or infarctions in more than one location were reported clinically in only 9 cases. The site of the infarction was described as "obscure" or "unknown" in 25 instances and "diffuse changes" were described in 50 instances. The initial infarction could be localized in 947 instances. Insofar as could be ascertained from the autopsy analysis, errors in localization were relatively few (see pp. 402–404).

Fifty-three per cent of all cases were described as having had an anterior, an anterolateral, or an anteroseptal infarction. Included in this figure are 7 per cent that involved both the anterior wall and the

TABLE 27

SITE OF ORIGINAL INFARCTION: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Original Infarctions in Various Locations

Site of Original Infarction	Number of Cases			Percentage of Cases		
	Total Sample	*Control Group*	*Treated Group*	*Total Sample*	*Control Group*	*Treated Group*
Cases with a single original infarction:						
Anterior or anterolateral	474	199	275	46.0	45.0	46.7
Anteroseptal	76	32	44	7.4	7.2	7.5
Total anterior	550	231	319	53.4	52.2	54.2
Posterior or posterolateral	369	163	206	35.8	36.9	35.0
Posteroseptal	13	8	5	1.3	1.8	.8
Total posterior	382	171	211	37.1	38.7	35.8
Septal	15	7	8	1.4	1.6	1.4
Diffuse changes	50	25	25	4.8	5.6	4.2
Site obscure or unknown[a]	25	6	19	2.4	1.4	3.2
Total cases with single original in- [illegible]	1022	440	582	99.1	99.5	98.8
[illegible] *total*[b]	9	2	7	.9	.5	1.2
Total cases	*1031*	*442*	*589*	*100.0*	*100.0*	*100.0*

[a] In 16 cases the EKG diagnosis was obscured by various types of bundle branch block; in 2 cases no [illegible] was based on clinical evidence only, EKG evidence of an in- [illegible] he location could not be classified from the EKG evidence; in [illegible] entricular tachycardia; and in 1 case the classification of the original infarction from EKG evidence is unreported.

[b] In these cases 2 infarctions apparently occurred approximately simultaneously, or two major areas were involved in a single infarction. The following sites were found in various combinations: 4 anterior, 1 anteroseptal, 6 posterior, 1 posteroseptal, and 6 diffuse changes.

TABLE 29

SEVERITY OF ILLNESS AT ONSET AND DURING COURSE, BY AGE: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Estimated to Have Been Severely Ill at Onset and during the Course of Their Illness, by Age

Age and Period Concerned	Total Sample: Number of Cases			Total Sample: Per Cent of Cases Severely Ill[a]	Control Group: Number of Cases			Control Group: Per Cent of Cases Severely Ill[a]	Treated Group: Number of Cases			Treated Group: Per Cent of Cases Severely Ill[a]
	Total	Illness Mild or Moderate	Illness Severe		Total	Illness Mild or Moderate	Illness Severe		Total	Illness Mild or Moderate	Illness Severe	
At onset:												
Under 40	26	16	10	*39*	9	4	5	—[b]	17	12	5	*29*
40-49	166	125	41	25	72	57	15	21	94	68	26	28
50-59	370	263	107	29	152	109	43	28	218	154	64	29
60-69	305	217	88	29	133	101	32	24	172	116	56	33
70-79	142	101	41	29	70	51	19	27	72	50	22	31
80-89	19	9	10	*65*	5	3	2	—[b]	14	6	8	*57*
Age unknown	3	3	—	—[b]	1	1	—	—[b]	2	2	—	—[b]
All ages	1031	734	297	29	442	326	116	26	589	408	181	31
During course:												
Under 40	26	18	8	*31*	9	5	4	—[b]	17	13	4	*24*
40-49	166	138	28	17	72	59	13	18	94	79	15	16
50-59	370	298	72	20	152	121	31	20	218	177	41	19
60-69	305	224	81	27	133	91	42	32	172	133	39	23
70-79	142	93	49	35	70	43	27	39	72	50	22	31
80-89	19	9	10	*65*	5	3	2	—[b]	14	6	8	*57*
Age unknown	3	3	—	—[b]	1	1	—	—[b]	2	2	—	—[b]
All ages	1031	783	248	24	442	323	119	27	589	460	129	22

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable*

[a] Based on total number of cases in each age group.

[b] Not computed since there were fewer than 10 cases in the sample.

group When this imbalance is subjected to a simple sign test of significance, it is found that this also could well have been a chance phenomenon, although the probabilities do not favor this interpretation.*

Hospitals ranged from 15 to 51 per cent in the proportion of their patients they estimated to have been severely ill at onset. In view of the small samples involved and the nature of the categories, it is not possible to tell whether the severity of cases differed substantially between hospitals, or whether the definition of severity varies, or whether the variations were in the main due to chance. Probably all factors contributed. The data are therefore not reported in detail.

* This test fails to give weight to the fact that the discrepancies tended to be greater in hospitals reporting more severe cases in the treated group than for those reporting more severe cases in the control group.

Severity during Course Compared with Severity at Onset

A difference of special interest in relation to anticoagulant therapy appears when severity at onset is compared with severity during the course. *Of the 326 patients reported to have been either mildly or moderately ill at*

larly to have been "mild" or "moderate" in 76 per cent of the total series, and "severe" in 24 per cent. The details appear in Table 29 and Figure 16.

A somewhat higher percentage of treated than control patients were considered to have been severely ill at the onset of the illness, the percentages being 31 per cent and 26 per cent respectively. While this difference is not statistically significant at the significance level adopted for this study, the contrast, when considered in conjunction with other evidence, suggests that doctors occasionally arranged by some circumvention for the inclusion of some severely ill cases in the treated group (see p. 9). The higher incidence of severe cases in the treated group weights the chance for uncomplicated recovery against this group since both deaths and thromboembolic complications were substantially more frequent among cases severe at onset. This type of selection clearly does not favor the treated group.

Data by hospitals again suggest that some severely ill patients were placed in the treated group because of the severity of their illness at onset. Eleven of the 16 cooperating hospitals were found to have reported a higher percentage of severe cases in the treated than in the control group and 5, a higher proportion of severe cases in the control

TABLE 28

SITE OF INFARCTION IN VARIOUS SERIES OF MYOCARDIAL INFARCTION: Percentage of Cases Reported to Have Had Recent Infarctions in Various Locations in This Series and in Several Series of Acute Coronary Occlusion with Myocardial Infarction Reported in the Literature

Site of Infarction	Percentage of Cases[a]					
	This Series	Mints and Katz[illegible]	Doscher and Poindexter[illegible]	Willius[illegible]	Yater *et al.*[illegible]	Yater *et al.*[illegible] (Autopsy Cases)
Anterior..	46.0	42.7	—	—	—	30.7[b]
Anterolateral..		3.8	—	—	—	—
Anteroseptal....	7.4	8.6	—	—	—	13.9
Total anterior.	53.4	55.1	53.9	44.8	44.0	44.6
Posterior.......	35.8	28.0	—	—	—	—
Posterolateral......		1.9	—	—	—	—
Posteroseptal..	1.3	5.9	—	—	—	—
Total posterior.	37.1	35.8	36.5	35.4	28.0	12.5[c]
Septal.......	1.4	—	—	—	—	13.1
Lateral.......	—	.4	—	—	14.0[d]	3.3
Not localized ..	7.2[e]	8.6[f]	7.0	19.8	14.0	26.7
No EKG......	—	—	2.7	—	—	—
Multiple...	.9	—	—	—	—	—
Total cases	100.	100.	100.	100.	100.	100.

[a] Based on total cases in series. Blank spaces indicate that classification was either not used or not needed.
[b] Includes "anterior wall" and "apex"
[c] Includes "posterior wall, left ventricle" and "posterior wall, right ventricle."
[d] Includes "lateral, anterolateral, posterolateral and anteroposterior."
[e] Includes "diffuse changes" and "site unknown."
[f] Includes "atypical" and "combined" (posterior pattern in limb leads and anterior pattern in chest leads).

in findings is probably to be explained by the fact that Russek and his co-workers equated "serious attacks" and "poor risk" cases although by definition "poor risk" includes a number of criteria for prognosis unrelated to the severity of the initial attack.

On the other hand, when severity is defined in the present study as the *severity of the course*, the findings do agree with those of Russek et al[108] that severity increases with age. The percentage of patients in the total sample and in the control and treated groups who suffered what was considered a *severe course* increased quite definitely with each decade of age (see Figure 18). The percentages for the eighth decade in each category were approximately twice those for the fifth decade.

From these data, it would appear, therefore, that in this particular study at least, there was no significant increase with advancing age in the percentage of patients who were obviously seriously ill at the onset of illness, but that there was a very definite progressive increase with advancing age in the percentage of patients who were seriously ill during the course of the illness. *This suggests that while older patients suffered attacks comparable in severity with younger patients, they did less well during the course of the illness.*

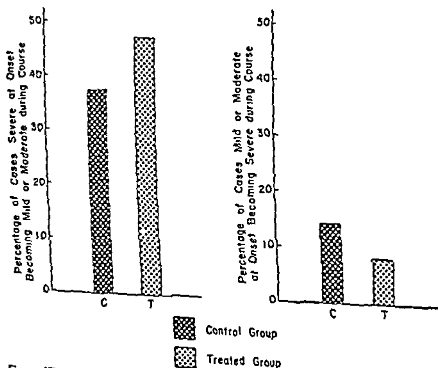


Figure 17. CHANGES IN SEVERITY OF ILLNESS: Percentage of cases in the control and treated groups estimated to have been severely ill at onset that became mildly or moderately ill during the course of the illness and similar percentages for cases estimated to have been mildly or moderately ill at onset that became severely ill during the course of the illness.

onset in the control group, 14 per cent showed a severe course, whereas of the 408 patients in the treated group reported mildly or moderately ill at onset, only 8 per cent became severely ill during the course (see Figure 17). The difference is statistically significant. A difference also appears in the course of the illness for patients classified as severe at onset. Of the 116 control group patients classified as severe at onset, 37 per cent showed a mild or moderate course, whereas of 181 treated cases found severe at onset, 47 per cent ultimately had a mild or moderate course (see Figure 17). The difference, though again suggestive, is not statistically significant, for relatively small numbers are involved. In consequence of the more favorable relation of the course to the condition at onset in the treated group, the proportion of patients severely ill dropped for the treated group from 31 per cent at onset to 22 per cent during the course, while the percentage severely ill in the control group remained at 27 per cent during the course as compared with 26 per cent at onset.

Severity of Illness by Major Age Groups

According to the data presented in Table 29 and Figure 18, the percentage of patients in the total sample who suffered what was considered a *severe onset* did not increase with each decade of age. Among the patients in the control and treated groups, the percentage exhibiting a severe onset increased only very slightly with age and in an inconsistent manner. This inconsistency may be attributed to the highly subjective nature of the observations reported and to the effects of chance, and perhaps also to unevenly applied efforts to secure anticoagulant therapy for severe cases.

This finding is not consistent with the conclusion of Russek et al.[208] that serious attacks are more frequent at the older age levels, "probably as a result of senile deterioration of the myocardium." The difference

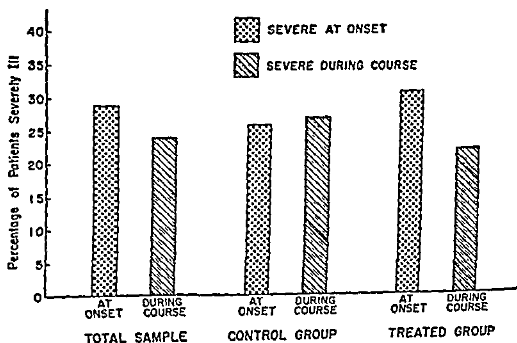


Figure 16. SEVERITY OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups estimated to have been severely ill at onset and during course of the illness.

Severity at Onset and History of Previous Myocardial Infarction

An attempt was also made to correlate the severity at onset with the history of a previous myocardial infarction, as shown in Table 30 and in Figure 19. Among the patients in the total sample experiencing no previous infarctions, one previous infarction and two or more previous infarctions, there was a slight but steady increase in the percentage of patients experiencing a severe onset in the present illness. This trend was very evident among treated patients, but was not apparent in the control group. In fact, a slightly smaller percentage of patients in the control group with a history of one previous infarction had a severe onset than did those who did not have a history of any previous infarctions.

This difference between the two groups suggests that among severely ill patients, those with a history of a previous infarction were more frequently switched to the treated group than were seriously ill patients without such a history. Apparently, a record of a previous infarction was considered an additional indication of urgency in such decisions. This selection obviously would tend to weight outcomes against the treated group. As will be shown later, however, the outcomes were better for the treated than the control group in spite of this initial handicap.

SYMPTOMS OF THE PRESENT ILLNESS

Pain

Incidence

A statement was made concerning the presence or absence of pain in all but one

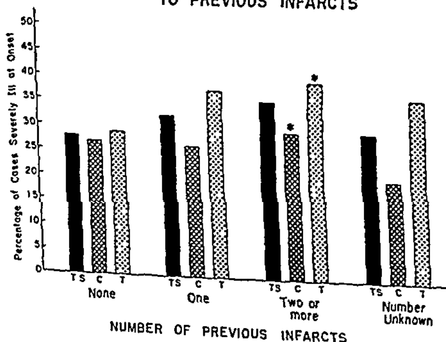


Figure 19. SEVERITY AT ONSET IN RELATION TO PREVIOUS INFARCTS: Percentage of cases in the total sample and in the control and treated groups whose illness was estimated to have been severe at onset among patients reported to have had one or more previous myocardial infarctions and among those reported to have had none prior to the present illness.

SEVERITY OF ILLNESS, BY AGE

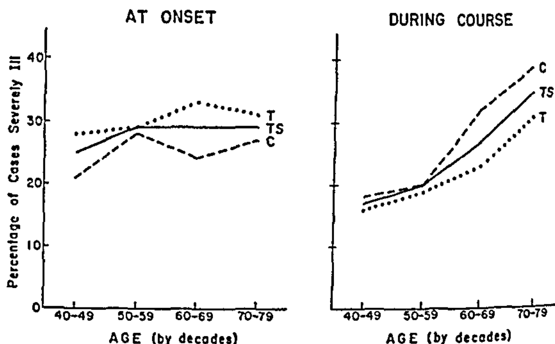


Figure 18. SEVERITY OF ILLNESS, BY AGE: Percentage of cases in the total sample and in the control and treated groups estimated to have been severely ill at onset and during the course of their illness, by age.

TABLE 30

SEVERITY AT ONSET, BY HISTORY OF PREVIOUS INFARCTIONS: Number and Percentage of Cases Estimated to Have Been Severely Ill at Onset among Patients in the Total Sample and in the Control and Treated Groups Reported to Have Had One or Two or More Previous Myocardial Infarctions and Those Reported to Have Had No Previous Infarctions

Number of Previous Infarctions	*Total Sample*				*Control Group*				*Treated Group*			
	Number of Cases			Per Cent of Cases Severe at Onset[a]	Number of Cases			Per Cent of Cases Severe at Onset[a]	Number of Cases			Per Cent of Cases Severe at Onset[a]
	Total	Cases Mild or Moderate at Onset	Cases Severe at Onset		Total	Cases Mild or Moderate at Onset	Cases Severe at Onset		Total	Cases Mild or Moderate at Onset	Cases Severe at Onset	
No previous infarctions .	740	535	205	28	313	229	84	27	427	306	121	28
One previous infarction	182	124	58	32	82	61	21	26	100	63	37	37
Two or more previous infarctions	40	26	14	*35*	17	12	5	*29*	23	14	9	*39*
Number of previous infarctions unknown	69	49	20	29	30	24	6	20	39	25	14	36
Total cases . .	1031	734	297	29	442	326	116	26	589	408	181	31

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on total number of cases with given number of previous infarctions.

tom in 91 per cent; but ensued rapidly in the other 9 per cent.

As demonstrated in Table 32, the incidence of pain is 90 per cent or more in most reported series of cases of coronary occlusion with myocardial infarction. It is curious, however, that in those series reported by Bean,[15] Saphir et al.,[111] Davis,[50] and by Herrmann and Decherd,[86] the incidence of painless coronary occlusion was considerably greater than in most series. It is presumed that the great majority of cases reported to have been without pain in these various series represent instances of "silent coronary occlusion."

Davis[50] noted that among his patients with painless occlusion the onset of the attack tended to be sudden and characterized by severe dyspnea. Other authors have noted that pain is apt to be absent when dyspnea and congestive heart failure are important initial symptoms On the other hand, Bean[15] and Smith, Rathe and Paul[119] reported that pain does occur in those instances where dyspnea and congestive heart failure are prominent symptoms. This follows logically in those series where pain occurs in nearly every case. It is possible that pain in severe degree is masked initially in those patients who suffer severe immediate congestive heart failure and/or shock, but that it becomes more apparent as congestive heart failure and shock are ameliorated and the patient's sensorium improves.

Severity of Pain

The degree of pain experienced by each patient is a highly subjective matter and the grading of it, from 1 to 4 degrees based upon an arbitrary classification, interpreted by a variety of observers, and recorded only according to the maximum degree of pain (which may have varied widely over a period of time), is open to criticism. It is of

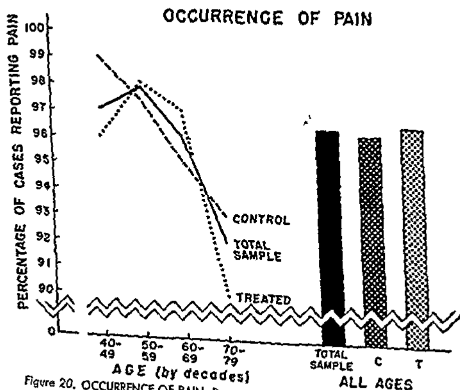


Figure 20. OCCURRENCE OF PAIN: Percentage of cases in the total sample and in the control and treated groups reported to have experienced pain of any degree during the six-week period of observation, by age.

case in this series. Pain was experienced at some time by 96 per cent of the patients. Pain did not occur in 4 per cent, these apparently representing the so-called "silent coronary occlusion." The percentage experiencing pain was the same in both the control and treated groups.

Pain was predominantly an initial symptom. It was present during the first week in 96 per cent, whereas it was experienced by only 20 per cent in later weeks. While the control and treated groups were the same with respect to the presence of pain in the first week, in later weeks, only 18 per cent of the treated group, but 22 per cent of the control group, experienced pain. While this difference is not statistically significant, it may, nevertheless, reflect indirectly the reduced rate of extensions and new infarctions in the treated group (see Chapter VIII).

When the incidence of pain among the patients in this series is tabulated by decade of age, as in Table 31 and Appendix F Table 7, or charted as in Figure 20, it is evident that there is a small, but definite decrease in the percentage of patients experiencing pain of any degree with advancing age. Patients up through the seventh decade of life experienced pain in more than 95 per cent of instances, while patients older than 70 years experienced pain in from 90 to 95 per cent of the attacks studied. The samples of patients younger than 40 years and older than 80 years are too small to permit valid analysis. Whether older patients are less apt to experience pain, or whether their sensibility to pain is less, is open to question.

It is recognized generally that pain is the outstanding symptom of acute coronary occlusion with myocardial infarction, occurring in the vast majority of patients and being commonly the most dramatic symptom experienced. Yater et al.[214] observed that, *in their young patients*, pain was the most common symptom both at the onset of the attack and during the course of the attack, but was not always the first symptom.

Among Yater's 450 fatal cases, 208 patients died before a history could be obtained. Among the 242 fatal cases from whom a history was obtained, pain was present in 236, absent in 6. Among the 400 survivors in Yater's series, pain was the most noteworthy symptom in 99 per cent. Therefore, among his 642 fatal and nonfatal cases from whom a history was obtained, pain occurred in 98 per cent. Among those with pain, it was the primary or first symp-

TABLE 31

OCCURRENCE OF PAIN. Percentage of Cases in the Total Sample and in the Control and Treated Groups Experiencing Pain of Any Degree during the Six-Week Period of Observation, by Age

Treatment Group	Percentage of Cases Experiencing Pain[a]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
Total sample	96	*100*	97	98	96	92	*95*	—[b]
Control group	96	—[b]	99	97	95	93	—[b]	—[b]
Treated group	96	*100*	96	98	97	90	*93*	—[b]
	Number of Cases with Report on Pain							
Total sample	1030	26	166	369	305	142	19	3
Control group	441	9	72	151	133	70	5	1
Treated group	589	17	94	218	172	72	14	2

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on number of cases with a report on pain

[b] Not computed since there were fewer than 10 cases in the sample.

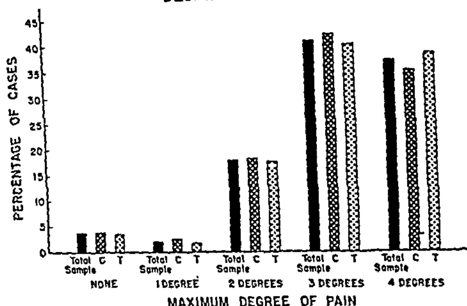


Figure 21. DEGREE OF PAIN: Percentage of cases in the total sample and in the control and treated groups experiencing maximum pain of various degrees during the six-week period of observation.

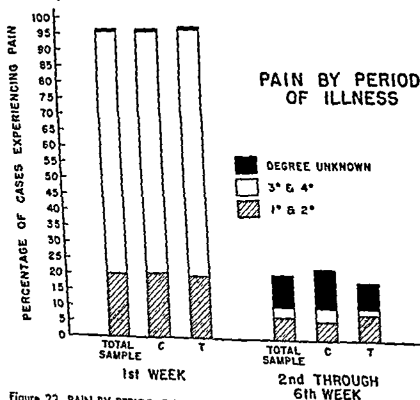


Figure 22. PAIN BY PERIOD OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups experiencing maximum pain of various degrees during the first week and from the second through the sixth week of observation.

interest, however, as a factor in interpreting this symptom on a comparative basis.

Reference to Table 33 (based on Appendix F, Table 7) and to Figure 21 reveals that, as might be expected, only 2 per cent of patients for whom the presence or absence of pain was reported experienced mild pain (one degree); 17 per cent, mild to moderate pain (two degrees); 40 per cent, moderate to severe pain (three degrees); and 36 per cent, severe pain (four degrees). Thus, in over three-quarters of instances the maximum degree of pain experienced was graded three or four plus. In slightly less than 20 per cent of instances, it was graded only one or two plus. These data are compatible with common experience.

TABLE 32

OCCURRENCE OF PAIN IN SEVERAL SERIES OF MYOCARDIAL INFARCTION: Number and Percentage of Cases with and without Pain in This Series and in Several Series of Acute Coronary Occlusion with Myocardial Infarction Reported in the Literature

Author(s)	Number of Cases in Series in Which Presence or Absence of Pain Was Known	Number of Cases		Percentage of Cases	
		With Pain	Without Pain[a]	With Pain	Without Pain[a]
This series	1030	992	38	96	4
Kennedy[105]	200	192	8	96	4
Bean[15]	—				
First attack	104	—[b]	—[b]	75	25
Second attack	40	—[b]	—[b]	66	34
Herrmann & Decherd[46]	127	95	32	75	25
Babey[10]	116	115	1	99	1
Pollard & Harvill[109]	375	353	22	94	6
Rosenbaum & Levine[108]	208	—[b]	—[b]	97	3
Kugel[109]	350	—[b]	—[b]	97	3
Mintz & Katz[183]	572	554	18	97	3
Saphir *et al.*[111]	34	21	13	62	38
Davis[50]	76	47	29	62	38
Yater *et al.*[115]	642	632	10	98	2
Howard[55]	165	—[b]	—[b]	93	7

[a] Also referred to as "silent coronary occlusion."

[b] Actual number not reported.

Comparison of the percentage of cases experiencing various maximum degrees of pain in the control and treated groups in the same table and figure reveals no significant differences. No inference regarding the effect of anticoagulant therapy on the occurrence of pain or the severity of pain in coronary occlusion with myocardial infarction can be drawn from figures for the total period of observation since only maximum degrees of pain were reported and these were usually experienced at the onset of the acute episode before anticoagulant therapy was initiated.

A tabulation (see Appendix F, Table 8) of the maximum degree of pain in later weeks as compared with the first week showed that while pain was predominantly of three or four plus degrees in the first week, in later weeks about two-thirds of those for whom pain of known degree was reported showed only one or two degrees of pain at the point of maximum pain after the first week. The

TABLE 33

DEGREE OF PAIN, BY TREATMENT GROUPS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Experiencing Maximum Pain of Various Degrees during the Six-Week Period of Observation

Maximum Degree of Pain Reported at Any Time[a]	Percentage of Cases[b]		
	Total Sample	Control Group	Treated Group
No pain	4	4	4
One degree of pain	2	2	2
Two degrees of pain	17	18	17
Three degrees of pain	40	41	39
Four degress of pain	36	34	37
Degree of pain unknown	1	1	1
Total with report on pain	100	100	100
	Number of Cases with Report on Pain		
Total cases	1030	441	589

[a] The types of pain counted include: retrosternal, shoulder, arm, neck, back, and epigastric pain and chest tightness.

[b] Based on number of cases with a report on pain.

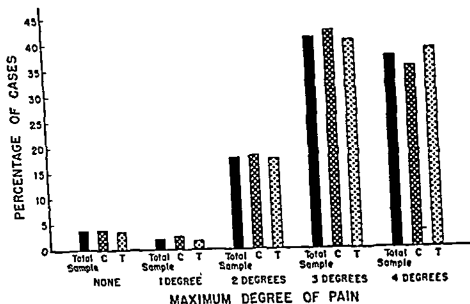


Figure 21. DEGREE OF PAIN: Percentage of cases in the total sample and in the control and treated groups experiencing maximum pain of various degrees during the six-week period of observation.

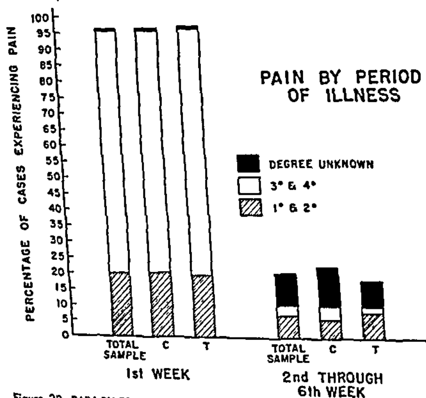


Figure 22. PAIN BY PERIOD OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups experiencing maximum pain of various degrees during the first week and from the second through the *sixth* week of observation.

treated group showed slightly milder pain than the control group, as well as a lower proportion with any pain, but the difference must be considered suggestive only since in many cases the degree of pain in later weeks was not reported. These facts are demonstrated in Figure 22 in which also is shown the close similarity between the control group and the treated group in respect to the incidence of pain of mild to moderate degree and of moderate to severe degree both during the first week and during later weeks of the illness.

It is evident from the data presented in Table 34 (based on Appendix F, Table 7) and in Figure 23 that, between the ages of 40 and 80 years, the percentage of patients experiencing severe pain, graded four plus, tends to decrease with age, and that for patients experiencing milder degrees of pain, to increase slightly. It appears that older patients suffering an attack of coronary occlusion with myocardial infarction are not only less apt to suffer pain than are younger patients, but the maximum pain which they do experience tends to be less severe as judged by the attending physician.

Yater et al.[244] found, *in their young men*, that the number of patients suffering pain of various degrees of severity was as follows:

Degree of Pain	Number of Cases	
	Fatal Cases	Survivors
None..	—	4
Mild	4	24
Moderate	17	54
Severe	84	305
Degree unknown..	137	13
Total cases observed	242	400

Dyspnea

Incidence

There was no evidence that dyspnea was experienced at any time by about 50

TABLE 34

DEGREE OF PAIN, BY AGE · Percentage of Cases in the Total Sample Experiencing Maximum Pain of Various Degrees during Six-Week Period of Observation, by Age

Maximum Degree of Pain Reported at Any Time[a]	Percentage of Cases[b]							
	All Ages	*Under 40*	40–49	50–59	60–69	70–79	*80–89*	Age Unknown
No pain	4	—	3	2	4	8	*5*	—[c]
One degree of pain	2	—	1	2	2	3	—	—[c]
Two degrees of pain	17	*19*	14	17	19	19	*16*	—[c]
Three degrees of pain	40	*42*	38	44	38	39	*21*	—[c]
Four degrees of pain	36	*39*	43	35	35	31	*53*	—[c]
Degree of pain unknown	1	—	1	—[d]	2	—	*5*	—[c]
Total with report on pain	100	*100*	100	100	100	100	*100*	—[c]
	Number of Cases with Report on Pain							
Total cases	1030	26	166	369	305	142	19	3

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] The types of pain counted include: retrosternal, shoulder, arm, neck, back, and epigastric pain and chest tightness.

[b] Based on number of cases with a report on pain.

[c] Not computed since there were less than 10 cases in the sample.

[d] Less than 0.5 per cent.

per cent of the 1022 patients for whom a report on dyspnea was available. Since the master forms did not require the separate reporting of orthopnea, paroxysmal dyspnea, or Cheyne-Stokes respiration, no separate counts of these were possible. The figures quoted for dyspnea include all degrees of severity and of duration. Among the patients with a report on this point, 54 per cent of the control group and 48 per cent of the treated group had experienced dyspnea. The difference is not statistically significant.

Dyspnea, like pain, was primarily an early symptom. Of the total sample, 48 per cent experienced dyspnea in the first week of their illness, but only 13 per cent after the first week. During this later period, only 11 per cent of the treated group experienced dys- greater in the treated than in the control group. This difference in later weeks is of borderline significance statistically and may again reflect indirectly the reduced incidence of extensions and secondary myocardial infarctions under anticoagulant therapy although the slightly lower treated group rate initially may also be a factor. When the percentage of cases experiencing various maximum degrees of dyspnea during the first week and during later weeks of the illness are compared, as in Appendix F Table 8 and in Figure 24, it is apparent that there is no great difference between the patients in the control group and those in the treated group, either during the first or in later weeks.

The incidence of dyspnea among the patients in this series is tabulated by decade of age in Table 35 and in Appendix F, Table 7, and charted in Figure 25. The data show a progressive increase in the percentage of

DEGREE OF PAIN BY AGE

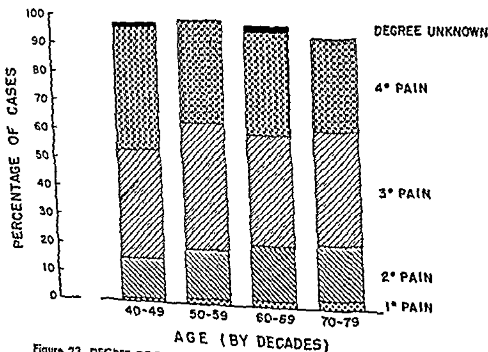


Figure 23. DEGREE OF PAIN BY AGE. Percentage of cases in the total sample experiencing maximum pain of various degrees during the six-week period of observation, by age.

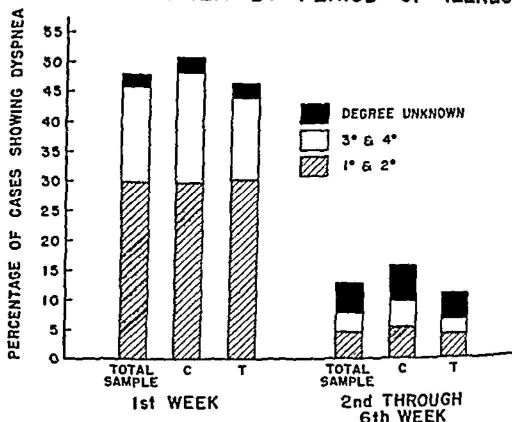


Figure 24. DYSPNEA BY PERIOD OF ILLNESS: *Percentage of cases in the total sample and in the control and treated groups experiencing maximum dyspnea of various degrees during the first week and from the second through the sixth week of observation.*

TABLE 35

OCCURRENCE OF DYSPNEA: Percentage of Cases in the Total Sample and in the Control and Treated Groups Experiencing Dyspnea of Any Degree during the Six-Week Period of Observation, by Age

Treatment Group	Percentage of Cases Experiencing Dyspnea[a]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
Total sample	50	*46*	46	47	53	58	*65*	—[b]
Control group	54	—[b]	50	48	58	64	—[b]	—[b]
Treated group	48	*41*	43	47	49	53	*64*	—[b]
	Number of Cases with Report on Dyspnea							
Total sample	1022	26	166	368	301	139	19	3
Control group	436	9	72	151	129	69	5	1
Treated group	586	17	94	217	172	70	14	2

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on number of cases with a report on dyspnea.

[b] Not computed since there were fewer than 10 cases in the sample.

patients experiencing dyspnea with advancing age. Patients younger than 60 years experienced dyspnea in somewhat more than 45 per cent of instances. Thereafter, there was a fairly steady increase in dyspnea to a level of approximately 60 per cent in the eighth decade. This increasing prevalence of dyspnea with age may be related to the more common occurrence of congestive heart failure among the older patients, but such factors as the increasing occurrence of senile emphysema may play a role.

The incidence of dyspnea in this series is comparable to that reported in several series in the literature, although Bean[15] reported that 95 per cent of his patients had experienced this symptom. Hamman[59] stated that dyspnea is seldom absent in patients suffering coronary occlusion with myocardial infarction, while Wolff and White[210] observed dyspnea in nearly all of the 23 cases observed and reported by them. Parkinson and Bedford[178] described a syndrome consisting of dyspnea and heart failure, but without pain, which they believed characterized one clinical group of patients with myocardial infarction. They described two other groups, in one of which the patient was overtaken by sudden death, while in the other, he developed anginal pain and shock. A comparison of the incidence of dyspnea in this series with that in certain other reports is made in Table 36.

Severity of Dyspnea

The severity of the dyspnea experienced by a given patient was estimated by the attending physician and reported by grading on a scale of one to four. It is obvious that the data provided are subject to considerable error and can be interpreted only on a broad scale. So highly subjective a symptom mani-

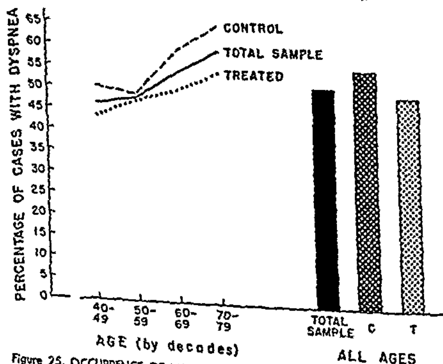


Figure 25. OCCURRENCE OF DYSPNEA: Percentage of cases in the total sample and in the control and treated groups reported to have experienced dyspnea of any degree during the six-week period of observation, by age.

fests itself with great variation among patients and is interpreted with difficulty by the observer.

Reference to Table 37 (based on Appendix F, Table 7) and to Figure 26 shows that, of all patients experiencing dyspnea, approximately one-fifth had suffered no more than one degree (mild), two-fifths had suffered two degrees (mild to moderate), slightly more than one-fifth had suffered dyspnea of three degrees (moderate to severe), and about one-eighth had suffered four degrees (severe). The degree of dyspnea was not known in about 5 per cent of cases in which this symptom was reported.

Thus, about 60 per cent of patients with dyspnea were reported to have had no more than mild to moderate dyspnea and about 35 per cent had moderate to severe dyspnea. Comparison of the percentage of cases experiencing various maximum degrees of dyspnea in the control and treated groups reveals no substantial differences.

From Table 38 (based on Appendix F, Table 7) and Figure 27, it is apparent that dyspnea not only becomes more common in coronary occlusion with myocardial infarction with advancing years, but that it tends to become more severe. Thus, in the fifth decade, 46 per cent of patients experienced dyspnea of whom about two-thirds suffered

TABLE 36

OCCURRENCE OF DYSPNEA IN SEVERAL SERIES OF MYOCARDIAL INFARCTION: Number and Percentage of Cases Experiencing Dyspnea in This Series and in Several Series of Acute Coronary Occlusion with Myocardial Infarction Reported in the Literature

Author(s)	Number of Cases Observed	Number of Cases with Dypsnea	Percentage of Cases with Dyspnea
This series	1022[a]	514	50
Howard[85]	165	64	39
Smith, Rathe & Paul[119]	420		
Dyspnea		189	45
Paroxysmal dyspnea		35	8
Rosenbaum & Levine[108]	208	148	71
Fisher & Zukerman[62]	108		
Dyspnea		59	55
Orthopnea		5	5
Bean[15]	300		
Initial attack			
Dyspnea		114	95
Orthopnea		66	68
Cheyne-Stokes		25	24
Second attack			
Dyspnea		67	96
Orthopnea		37	63
Cheyne-Stokes		25	71
Yater *et al.*[255]			
Fatal attacks	242		
Primary symptom		20	8
A main symptom[b]		159	66
Survivors	400		
Primary symptom		37	9
A main symptom[b]		216	54
Total cases	642		
Primary symptom		57	9
A main symptom[b]		375	58

[a] Excluding those in which status of dyspnea was not reported.

[b] Includes dyspnea, cough, and rales.

TABLE 37

DEGREE OF DYSPNEA, BY TREATMENT GROUPS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Experiencing Maximum Dyspnea of Various Degrees during the Six-Week Period of Observation

Maximum Degree of Dyspnea Reported at Any Time	Percentage of Cases[a]		
	Total Sample	Control Group	Treated Group
No dyspnea	50	46	52
One degree of dyspnea	11	10	11
Two degrees of dyspnea	20	20	19
Three degrees of dyspnea	11	13	10
Four degrees of dyspnea	6	8	6
Degree of dyspnea unknown	2	3	2
Total with report on dyspnea	100	100	100
	Number of Cases with Report on Dyspnea		
Total cases	1022	436	586

[a] Based on number of cases with a report on dyspnea.

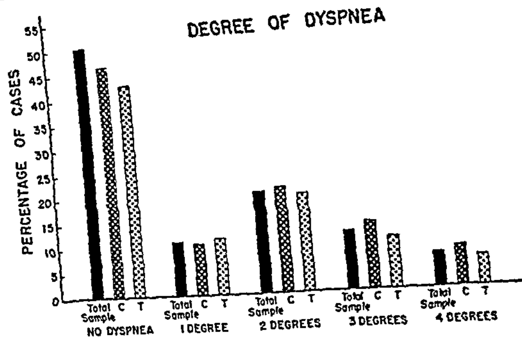


Figure 26. DEGREE OF DYSPNEA: Percentage of cases in the total sample and in the control and treated groups experiencing maximum dyspnea of various degrees during the six-week period of observation.

TABLE 38

DEGREE OF DYSPNEA, BY AGE: Percentage of Cases in the Total Sample Experiencing Maximum Dyspnea of Various Degrees during the Six-Week Period of Observation, by Age

Maximum Degree of Dyspnea Reported at Any Time	Percentage of Cases[a]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
No dyspnea	50	*53*	54	53	47	42	*37*	—[b]
One degree of dyspnea	11	*8*	10	12	9	9	*11*	—[b]
Two degrees of dyspnea	20	*27*	17	19	21	19	*26*	—[b]
Three degrees of dyspnea	11	*4*	11	8	13	19	*21*	—[b]
Four degrees of dyspnea	6	*8*	5	6	7	8	—	—[b]
Degree of dyspnea unknown	2	—	3	2	3	3	*5*	—[b]
Total with report on dyspnea	100	*100*	100	100	100	100	*100*	—[b]
	Number of Cases with Report on Dyspnea							
Total cases	1022	26	166	368	301	139	19	3

Note *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable*

[a] Based on number of cases with a report on dyspnea.

[b] Not computed since there were less than 10 cases in the sample

mild or mild to moderate dyspnea (1 degree to 2 degrees) and about one-third suffered moderate to severe, or severe dyspnea (3 degrees to 4 degrees). In contrast, among patients in the eighth decade, 58 per cent experienced dyspnea, of whom nearly one-half suffered moderate to severe or severe dyspnea (3 degrees to 4 degrees).

Vomiting

Of the 1024 patients with a report on vomiting, 30 per cent had experienced one or more episodes of vomiting. Reference to Table 39 (based on Appendix F, Table 9) and to Figure 28 reveals that the percentages vomiting in the control and treated groups were essentially similar (31 and 29 per cent respectively) and that there were no marked variations in the percentage of patients of different ages who experienced vomiting during their illness.

From Table 40 and Figure 29, it is further evident that there was no important difference in the occurrence of this symptom in the control and treated groups in either the first or later weeks.

Cases were also tabulated according to the day of their illness on which vomiting first occurred even though such vomiting may have reappeared on a later day. The following facts are illustrated in Figure 30 (based on Appendix F, Table 10). Vomiting occurred on the first day of the illness in over two-thirds of those vomiting (for whom the day of onset of vomiting was known). After the first day, the onset of vomiting fell off very rapidly. Over 97 per cent of patients who vomited at any time did so before the end of the first week of illness. Only 8 patients vomited for the first time after the first week, while 6 others developed recurrence of vomiting during the later weeks of the illness.

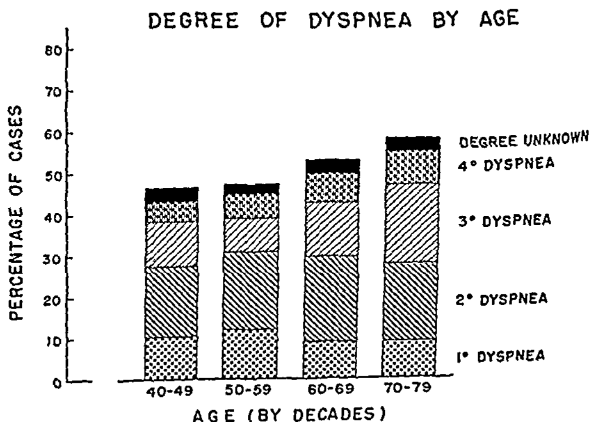


Figure 27. DEGREE OF DYSPNEA BY AGE: *Percentage of cases in the total sample experiencing maximum dyspnea of various degrees during the six-week period of observation, by age.*

TABLE 39

OCCURRENCE OF VOMITING: *Percentage of Cases in the Total Sample and in the Control and Treated Groups Vomiting Any Time during the Six-Week Period of Observation, by Age*

Treatment Group	Percentage of Cases Vomiting[a]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
Total sample	30	*23*	28	30	31	30	*32*	—[b]
Control group	31	—[b]	32	32	33	26	—[b]	—[b]
Treated group	29	*18*	26	28	30	33	*29*	—[b]
	Number of Cases with Report on Vomiting							
Total sample	1024	26	166	368	303	139	19	3
Control group	437	9	72	150	131	69	5	1
Treated group	587	17	94	218	172	70	14	2

Note: *Italics are used when percentages quoted have less than 50 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on number of cases with a report on vomiting.

[b] Not computed since there were less than 10 cases in the sample.

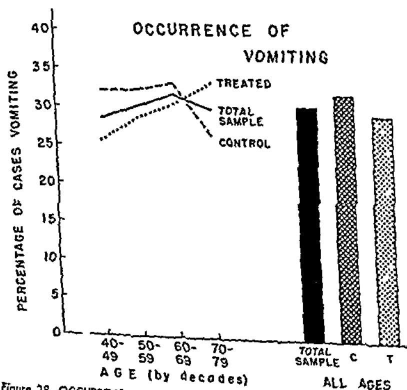


Figure 28. OCCURRENCE OF VOMITING: Percentage of cases in the total sample and in the control and treated groups developing vomiting at any time during the six-week period of observation, by age.

Parkinson and Bedford[175] stated that vomiting is usual after the onset of myocardial infarction and that it is sometimes repeated for days. Hamman[80] noted that vomiting is associated frequently with instances of occlusion in which epigastric pain and associated gastrointestinal symptoms occur. The occurrence of vomiting in our series approximates closely that reported by Yater et al.[245] and by Howard[95] but is somewhat less than that reported by Bean,[15] as shown by reference to Table 41.

SIGNS OF THE PRESENT ILLNESS

Friction Rub

When an area of myocardial infarction extends to the visceral pericardium, pericarditis develops. When this area of acute pericarditis is small, and particularly when it involves only the posterior surface of the heart, a friction rub may not be audible. Furthermore, an audible friction rub is notoriously transient in duration and often faint in intensity. It may be missed or overlooked in a considerable percentage of those patients in whom it occurs. It may be masked readily by extracardiac pathological changes, particularly those of pleural origin. For these reasons, the incidence of friction rub reported in the literature is undoubtedly minimal.

TABLE 40

VOMITING, BY PERIOD OF ILLNESS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Vomiting Any Time during the First Week and Any Time during the Second through the Sixth Week of Observation

Treatment Group	Percentage of Cases Vomiting[a] 1st Week	Percentage of Cases Vomiting[a] 2nd through 6th Week[b]
Total sample	29	1
Control group	30	2
Treated group	28	1
	Number of Cases with Report on Vomiting during Period	
Total sample	1024	952
Control group	437	405
Treated group	587	547

[a] Based on number of cases with reports on vomiting.

[b] Symptoms from the second through the sixth week were doubtless underreported.

Among the 1016 cases with a report on this subject, a rub was heard on one or more occasions in 15 per cent. There was no significant difference between the control and treated groups in the percentage of patients in whom a friction rub was heard, the percentages being 14 and 15 respectively. The extent to which these clinical observations of friction rub correlated with an autopsy finding of pericarditis is discussed in Chapter XIII.

The incidence of recognized friction rub in the total sample and in the control and treated groups is tabulated by decade of age in Table 42 (based on Appendix F, Table 9) and presented graphically in Figure 31. The variations from decade to decade were not great and are probably without significance.

The incidence of a recognized friction rub in this series is compared with the incidence reported by various other observers in Table 43. Although the percentage of cases in which a friction rub was heard extends over a range of from less than 1 per cent[116] to 20 per cent,[116] *the tabulated data suggest that clinically audible friction rubs are generally recognized in about 16 per cent of patients.*

Of considerable interest is the temporal relationship between the time at which a friction rub was first heard and the onset of the illness. The data are tabulated in Appendix F, Table 11 and summarized and presented graphically in Figure 32. The curve of the graph shows clearly that the number of instances in which a friction rub was first heard increased rapidly during the first three days and then fell off less sharply through the first week. The number of cases in which a friction rub was first heard during

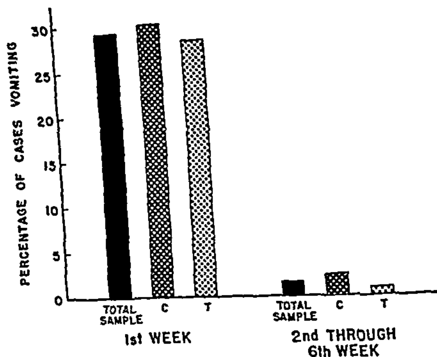


Figure 29. VOMITING BY PERIOD OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups vomiting any time during the first week and from the second through the sixth week of observation.

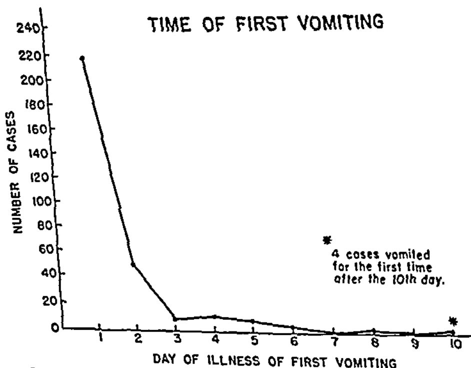


Figure 30. TIME OF FIRST VOMITING- Number of cases in the total sample vomiting for the first time on various days of their illness.

TABLE 41

OCCURRENCE OF VOMITING IN SEVERAL SERIES OF MYOCARDIAL INFARCTION: Number and Percentage of Cases Vomiting in This Series and in Several Series of Acute Coronary Occlusion with Myocardial Infarction Reported in the Literature

Author(s)	Number of Cases Observed	Number of Cases Vomiting	Percentages of Cases Vomiting
This series	1024[a]	306	30
Yater *et al.*[244b]			
Symptoms at onset:			
Fatal cases	242	25	10
Survivors	400	17	4
Total cases	642	42	7
Main symptoms of attack:			
Fatal cases	242	99	41
Survivors	400	134	34
Total cases	642	233	36
Bean[14]	300		
First attack		47	59
Second attack		16	59
Howard[11]	165	—[c]	28

[a] Includes cases with report on status of vomiting.
[b] Nausea, vomiting or both.
[c] Actual number not reported.

the eighth through the tenth days was small and relatively constant. Daily figures were not tabulated beyond the tenth day, but in only ten instances was a friction rub first noted after the tenth day, probably as the result of pericarditis due to secondary myocardial infarction rather than to delayed pericardial reactions to the initial infarction. Yater et al.[244] reported that among his 400 survivors, transient friction rubs were heard during or shortly after the attack in 11 patients (3 per cent), and later in an additional 17 patients (4 per cent), a total of 28 patients (7 per cent of cases).

Cardiac Enlargement

In connection with the following discussion of cardiac enlargement, it is recognized that slight degrees of enlargement are difficult to determine by either physical or roentgen examination and that a transverse position of the heart within the thorax may suggest enlargement which does not exist. Furthermore, cardiac enlargement representing largely cardiac dilatation may be relatively transient in nature and so may often be missed. For these reasons, the validity of

TABLE 42

OCCURRENCE OF FRICTION RUB: Percentage of Cases in the Total Sample and in the Control and Treated Groups Developing a Recognized Pericardial Friction Rub at Some Time during the Six-Week Period of Observation, by Age

Treatment Group	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
	Percentage of Cases Developing a Recognized Friction Rub[a]							
Total sample	15	*23*	11	15	15	14	*21*	—[b]
Control group	14	—[b]	10	14	14	16	—[b]	—[b]
Treated group	15	*24*	13	16	17	12	*21*	—[b]
	Number of Cases with Known Friction Rub Status							
Total sample	1016	26	166	364	300	138	19	3
Control group	437	9	72	148	132	70	5	1
Treated group	579	17	94	216	168	68	14	2

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*
[a] Based on number of cases with known friction rub status.
[b] Not computed since there were fewer than 10 cases in the sample.

the following figures or an absolute basis is open to question. They may, however, be of some significance on a comparative basis.

Among the 1001 cases with a report *on this* point, cardiac enlargement was demonstrated at some time during the course *of the* present illness in 47 per cent. Fifty-one per cent of the *control* group and 44 per cent of the treated group showed enlargement some*time* during the illness. The difference is of borderline significance statistically and may reflect the influence of anticoagulant therapy or differences existing prior to therapy, or both. A discussion of differences of this nature will be found in the summary at the end of Chapter VI where all the data on signs, symptoms, and laboratory findings are coordinated.

Enlargement was known to have been present before the present illness in 8 per cent of the patients. It was observed for the first time during the first week of the present illness in 33 per cent, and during the second to the sixth week of observation, in 6 per cent (*see Appendix* F, Table 12 and Figure 33). As shown in Figure 33, there was no *important* difference in the percentage of cases in the control and the treated groups *first* observed to have cardiac enlargement during each of these three periods of time. However, the cumulative total *of cases* with enlargement in the first week and *in* later weeks was sufficiently different in the control and treated groups to be of borderline significance statistically. Since *one comparison* in twenty may be expected to show differences in excess of the 95 per cent confidence limits, this may still have occurred on a chance basis. The comparability of the samples is more fully evaluated in the summary at the end of Chapter VI.

As demonstrated in Table 44 and in Figure 34, the percentage of patients exhibiting cardiac enlargement at some time during the course of the present illness increased sharply with each decade of life, *from 21* per cent

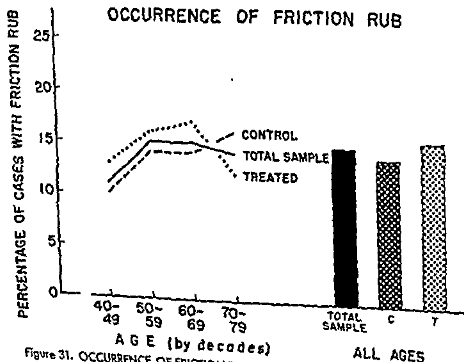


Figure 31. OCCURRENCE OF FRICTION RUB- Percentage of cases in the total sample and in the control and treated *groups developing* a recognized pericardial friction rub at some time during *the six-week* period of observation, by age.

among patients less than forty years of age to 66 per cent among patients in the eighth decade. The difference between the patients in the control and in the treated group in this respect was greater than in most other characteristics compared but was still only of borderline significance statistically. (See Appendix C for explanation of terms.)

The incidence of cardiac enlargement in patients suffering coronary occlusion with myocardial infarction, as reported in the literature, is high, but considerable variation is encountered when reports are compared. Frequently, the criteria by which the presence of cardiac enlargement is estimated are not stated. The relationship between cardiac hypertrophy and the presence of hypertension is often ignored.

Master, Dack and Jaffe[133] found that the presence of cardiac enlargement clinically among their patients with coronary occlusion and myocardial infarction was closely correlated with the occurrence of heart failure. Both cardiac enlargement and heart failure were more common in women than in men, a fact presumed to be due to the greater incidence of hypertension in women. Their figures are:

	Males	Females
Enlarged heart	58.1%	74.3%
Heart failure (2–4 plus)	50.4%	59.8%
Pulmonary edema	14.5%	20.5%

In their experience, the incidence of congestive heart failure and of cardiac enlargement increased with age and was uncommon among young patients.

Yater et al.[245] discuss the subject of cardiac enlargement in considerable detail. Among the young men with coronary disease studied by them, 450 patients died and were autopsied. The weight of the hearts of 374 of these were reported. Two hundred and thirty-two hearts, or 52 per cent, were hypertrophied and 70 hearts, or 16 per cent, were hypertrophied from grade two to four plus, based on the tables of normal weights of hearts correlated with body weight as prepared by H. L. Smith.[220] Hypertrophy was associated with a previous history of heart disease. Only 17 per cent of those patients without such a history had enlargement of from two to four plus while 34 per cent of those with a history of previous heart disease had such a degree of hypertrophy.

Yater et al. observed a high correlation with the duration of the terminal illness, since enlargement of grade two or more occurred in only 11 per cent of those patients who died within 24 hours of the onset of their attack, while 33 per cent of those who survived for more than 24 hours had this degree

TABLE 43

OCCURRENCE OF FRICTION RUB IN SEVERAL SERIES OF MYOCARDIAL INFARCTION: Number and Percentage of Cases in Which Audible Pericardial Friction Rubs Were Recognized in This Series and in Several Series of Acute Coronary Occlusion With Myocardial Infarction Reported in the Literature

Author(s)	Number of Cases Observed	Friction Rub Heard: Number of Cases	Friction Rub Heard: Percentage of Cases
This series	1016[a]	149	15
Bean[14]			
First attack		17	15
Second attack		7	6
Total	176	24	14
Yater et al.[245]	400 survivors	28[b]	7
Mintz and Katz[153]	572	26	5
Rosenbaum and Levine[204]	208	33	16
Levy[118]	50	10	20
Fisher and Zukerman[62]	108	1	1
Howard[88]	156	—[c]	10

[a] Includes cases in which the status of friction rub was known.

[b] Transient rub heard during or shortly after attack in 11 patients; later, in 17 additional patients.

[c] Not reported.

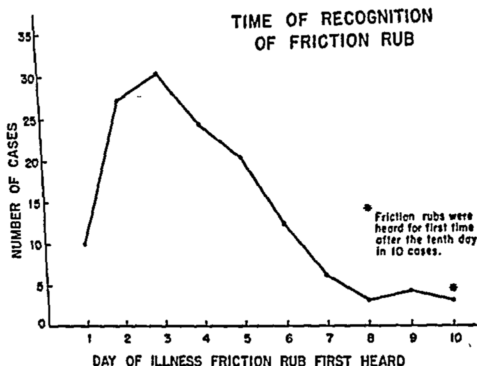


Figure 32. TIME OF RECOGNITION OF FRICTION RUB: Number of cases in the total sample developing a recognized pericardial friction rub for the first time on various days of their illness.

TIME OF RECOGNITION OF
CARDIAC ENLARGEMENT

PERCENTAGE OF CASES

0 5 10 15 20 25 30 35

TOTAL SAMPLE C T
Existing Prior to Illness

TOTAL SAMPLE C T
First Observed during 1st Week of Illness

TOTAL SAMPLE C T
First Observed 2nd through 6th Week

CARDIAC ENLARGEMENT

Figure 33. TIME OF RECOGNITION OF CARDIAC ENLARGEMENT: Percentage of cases in the total sample and in the control and treated groups first developing recognized cardiac enlargement before or during various periods of their illness.

TABLE 44

OCCURRENCE OF CARDIAC ENLARGEMENT: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Cardiac Enlargement during the Six-Week Period of Observation, by Age

Treatment Group	Percentage of Cases Showing Cardiac Enlargement[a]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
Total sample	47	*21*	26	47	52	66	*63*	—[b]
Control group	51	—[b]	29	50	54	71	—[b]	—[b]
Treated group	44	*18*	24	45	49	61	*57*	—[b]
	Number of Cases with Report on Cardiac Enlargement							
Total sample	1001	24	161	364	295	135	19	3
Control group	424	7	70	148	127	66	5	1
Treated group	577	17	91	216	168	69	14	2

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on number of cases with a report on cardiac enlargement.

[b] Not computed since there were fewer than 10 cases in the sample.

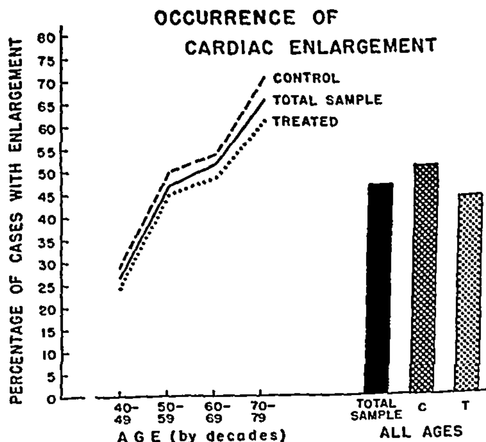


Figure 34. OCCURRENCE OF CARDIAC ENLARGEMENT: Percentage of cases in the total sample and in the control and treated groups showing cardiac enlargement during the six-week period of observation, by age.

of enlargement. Men dying with hypertrophy of grade two or more lived longer after fatal coronary occlusion than those with no hypertrophy or with a lesser degree. Forty-two per cent of those with hypertrophy of two plus or more lived 24 hours or more as against 12 per cent of those with no hypertrophy or less than 2 plus.

There was no relation between hypertrophy and the existence of hypertension at the time of military induction but the number of instances where hypertensives were inducted were *few*. *Only 16 patients* had hypertension at the time of the attack. There was no relation between cardiac hypertrophy and the occurrence of sclerotic occlusion or of thrombotic occlusion, but there was an association of cardiac hypertrophy with the occurrence of infarction Among those found at autopsy to have hearts of various sizes, the following percentages showed gross or microscopic infarctions:

Infarction	Normal size or hypertrophy less than 2 plus (380 cases)	Hypertrophy 2 plus or more (70 cases)
Gross	20.2%	50 0%
Microscopic	5 3%	4.3%
Any infarction (total)	25.5%	54.3%

The incidence of infarction was thus twice as great among those with hypertrophy of grades two to four as it was among those with no hypertrophy or less than two plus hypertrophy. More patients with hypertrophy of grades two *to four* had mural thrombi (21 per cent as against 8 per cent for patients with no *hypertrophy* or less than two plus hypertrophy)

Yater et al. conclude that myocardial degeneration does cause hypertrophy of the heart since hearts more seriously damaged by infarction or *scarring and* those with mural thrombi tended to be larger than those without these lesions but with coronary artery disease alone.

Parkinson and Bedford[173] have stated that coronary artery disease alone can cause some cardiac hypertrophy, especially of the left ventricle, but cardiac enlargement is not a feature of coronary artery disease unless hypertension or valvular disease are also present. In Yater's material, 70, or 16 per cent, of the hearts were enlarged "2 or more degrees" yet only 16 patients had hypertension and only 6 patients had valvular disease.

Davis and Blumgart[44] *postulated* that with severe coronary sclerosis, some hypertrophy occurs due *to poor nutrition* which causes muscle fibers to stretch. Hypertrophy *is greater* in cases with congestive heart failure. Yater agrees with this explanation and *states* that "We believe *our study* shows definitely that coronary artery disease alone *may lead* to hypertrophy."

Yater et al.[155] found no significant dilatation of the heart chambers in 80 per cent of their autopsy cases. Dilatation was slight *in* 9 per cent, moderate in 5 per cent and great in 1 per cent.

The incidence of cardiac hypertrophy in various *series* of cases of coronary artery disease in the literature ranges from 45 to 94 per cent. The *pertinent data* from several such series are summarized in Table 45.

Master, Garfield and Walters[111] found that enlargement of the heart not uncommonly occurred in *men with* coronary occlusion whose blood pressure was normal. They concluded that coronary artery disease without hypertension may cause enlargement of the heart. They found, on the contrary, that cardiac enlargement rarely occurred in women *who had* normal blood pressure. Hypertension, *they felt*, appeared to be an important factor in the production of cardiac enlargement in women.

Pulmonary Edema

The reporting and analysis of pulmonary edema was undertaken because of its importance as an evidence of *left* heart failure. Participants were requested to indicate the degree of severity of *pulmonary* edema on a

scale of four, but no criteria were provided upon which such an estimate could be based. Reporting was, therefore, arbitrary and can serve no more than as a crude estimate of the comparability of the samples in respect to this finding. On this basis, then, pulmonary edema of some degree was observed at some time during the six-week period in 27 per cent of the 1021 cases for whom a statement on this point was available.

Data by treatment groups and decade of age are presented in Table 46 (based on Appendix F, Table 13) and in Figure 35. Pulmonary edema was observed somewhat more frequently in the control than in the treated group, the percentages being 31 and 24 per cent respectively. The difference is of borderline significance statistically. The meaning of this and similar differences is discussed on pp. 176–177.

TABLE 45

OCCURRENCE OF CARDIAC ENLARGEMENT IN SEVERAL SERIES OF CORONARY ARTERY DISEASE: Number and Percentage of Cases Found to Have Cardiac Enlargement When Examined at Autopsy as Reported in the Literature for Several Series of Cases of Coronary Artery Disease

Author(s)	Number of Cases Observed	Cases with Cardiac Enlargement		Criteria for Hypertrophy	Comment
		Number	Per Cent		
Nathanson[149]........	113	68	60	*Over 400 gms.*	*Congestive failure more common in patients with large hearts.*
Barnes and Ball[13]....	49	—[a]	—[a]	—[a]	*Hearts tended to exceed average weights.*
Lisa and Ring[131]....	100	—[a]	—[a]	—[a]	Average weight of hearts 519 gms (range: 200-925 gms.).
Appelbaum and Nicolson[7].........	150 (weight known in 94)	69	73	Over 400 gms.	Majority of hearts weighed above average. Many patients had hypertension.
Woods and Barnes[219]	48	45	94	—[a]	Average weight 496 gms. (Average normal weight 330 gms.)
Bruenn, Turner & Levy[34].	338	236	70	—[a]	Average weight 543 gms.
Bean[16]..	300	252	84	Over 350 gms. in women, 400 gms. in men	"Majority of cases with cardiac infarction have enlarged hearts."
Yater *et al.*[266].....	450 (weight known in 374)	232	62	See text.	*Coronary artery disease alone may lead to hypertrophy.*

[a] Not reported.

TABLE 46

OCCURRENCE OF PULMONARY EDEMA: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Pulmonary Edema of Any Degree during the Six-Week Period of Observation, by Age

Treatment Group	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
	Percentage of Cases with Pulmonary Edema[a]							
Total sample	27	*8*	17	28	30	42	*32*	—[b]
Control group	31	—[b]	19	27	32	49	—[b]	—[b]
Treated group	24	*0*	15	25	28	35	*21*	—[b]
	Number of Cases with Report on Pulmonary Edema							
Total sample	1021	26	165	368	301	139	19	3
Control group	439	9	72	152	130	70	5	1
Treated group	582	17	93	216	171	69	14	2

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on the number of cases with a report on pulmonary edema.

[b] Not computed since there were fewer than 10 cases in the sample.

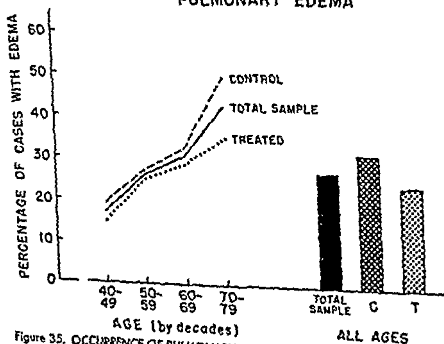


Figure 35. OCCURRENCE OF PULMONARY EDEMA: Percentage of cases in the total sample and in the control and treated groups showing pulmonary edema of any degree during the six-week period of observation, by age.

The slightly greater incidence of pulmonary edema in the control group is evident at all ages. In both treatment groups, there is a steady increase by decade of age in the percentage of cases exhibiting pulmonary edema. Among patients 70 to 79 years of age, this percentage was approximately two and one-half times that among patients 40 to 49 years of age.

When the occurrence of pulmonary edema is considered according to the maximum degree of severity reported, as in Table 47, Appendix F Table 13, and in Figure 36, it is evident that the majority of patients suffering this complication suffered it to a mild or moderate degree. Only 8 per cent of patients in the entire series exhibited pulmonary edema of a severe, or moderate to severe, degree. The control and treated patients experienced pulmonary edema of three and four plus to a similar extent, but the control patients experienced one and two plus pulmonary edema to a greater extent than did the treated patients, the percentages being 2 and 16 per cent respectively.

TABLE 47

DEGREE OF PULMONARY EDEMA, BY TREATMENT GROUPS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Pulmonary Edema of Various Degrees during the Six-Week Period of Observation

Maximum Degree of Pulmonary Edema Reported at Any Time	Percentage of Cases*		
	Total Sample	Control Group	Treated Group
None	73	69	76
Mild to moderate:			
One degree	8	10	7
Two degrees	10	12	9
Total mild to moderate	18	22	16
Moderate to severe:			
Three degrees	5	5	4
Four degrees	3	3	3
Total moderate to severe	8	8	7
Degree unknown	1	1	1
Total with edema	27	31	24
	Number of Cases with Report on Edema		
Total cases	1021	439	582

* Based on number of cases with a report on pulmonary edema.

When the occurrence of pulmonary edema of one and two degrees of severity are combined and those of three and four degrees are combined and the results examined by decade of age, as in Table 48 and in Figure 37, it is evident that there is a steady increase in the incidence of pulmonary edema of moderate to severe degree with each decade of advancing age. With pulmonary edema of mild to moderate degree there is an overall increase in incidence with advancing age, but not steadily. A levelling-off occurs between the sixth and the seventh decades, during which no significant change in the incidence of mild and mild to moderate pulmonary edema is observed.

Pulmonary edema is shown by period of illness in Table 49, Appendix F Table 14, and in Figure 38. There was a slightly greater incidence of pulmonary edema in the control than in the treated groups during comparable periods. In both periods, however, the difference was almost entirely in cases that developed pulmonary edema of grades one degree and two degrees. Pulmonary edema of a severity of three and four degrees was very closely similar in both periods.

Liver Enlargement

Liver enlargement, an important manifestation of right heart failure, was analyzed in the same manner as pulmonary edema. No attempt was made, however, to ascertain from the individual hospitals the exact criteria for a statement of hepatic enlargement nor was an attempt made to determine in each instance reported the cause for such enlargement, the assumption being that, in the

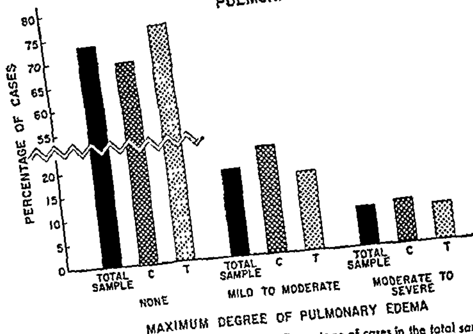


Figure 36. DEGREE OF PULMONARY EDEMA: Percentage of cases in the total sample and in the control and treated groups showing maximum pulmonary edema of various degrees *during* the six-week period of observation.

TABLE 48

... Showing ... Age

Maximum Degree of Pulmonary Edema Reported at Any Time	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
None	73	92	83	74	70	58	*68*	—[b]
Mild to moderate (1st or 2nd degree)	18	8	13	19	18	26	*16*	—[b]
Moderate to severe (3rd or 4th degree)	8	—	4	6	10	14	*16*	—[b]
Degree unknown	1	—	—	1	2	2	—	—[b]
Total with report on pulmonary edema	100	*100*	100	100	100	100	*100*	—[b]
	Number of Cases with Report on Pulmonary Edema							
Total cases	*1021*	*26*	*165*	*363*	*301*	*139*	*19*	*3*

Note: *Italics are used when percentages quoted have less than 50 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on number of cases with a report on pulmonary edema.

[b] Not computed since there were less than 10 cases in the sample.

majority of instances, such enlargement would be due to congestive changes. Furthermore, it is realized that the recognition of hepatic enlargement on the basis of physical examination is prone to considerable error except in those instances where enlargement is very great. The findings must therefore be considered approximate only.

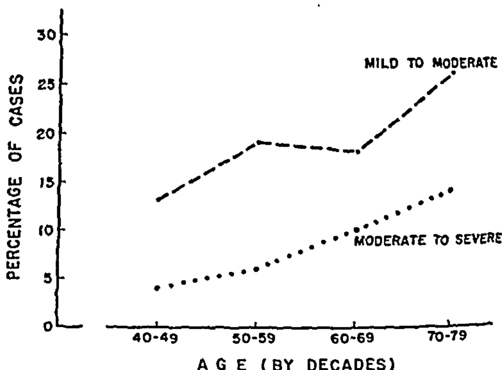


Figure 37. DEGREE OF PULMONARY EDEMA BY AGE: Percentage of cases in the total sample showing maximum pulmonary edema of various degrees during the six-week period of observation, by age.

TABLE 49

DEGREE OF PULMONARY EDEMA, BY PERIOD OF ILLNESS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Pulmonary Edema of Various Degrees during the First Week and from the Second through the Sixth Week of Observation

Maximum Degree of Pulmonary Edema Reported at Any Time	Percentage of Cases*					
	1st Week			2nd through 6th Week		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
None	77	74	79	87	86	88
Mild to moderate (1st or 2nd degree)	16	19	14	7	8	6
Moderate to severe (3rd or 4th degree)	6	6	6	3	2	3
Degree unknown	1	1	1	3	4	3
Total with report on pulmonary edema	100	100	100	100	100	100
	Number of Cases with Report on Pulmonary Edema					
Total cases at beginning of the period	1016	436	580	938	404	534

* Based on number of cases with a report on pulmonary edema.

Some degree of hepatic enlargement was reported in 163 instances, or 16 per cent of all cases with a report on this point (1011 cases). As shown in Table 50 (based on Appendix F, Table 13) and in Figure 39, a somewhat higher percentage of control cases exhibited hepatic enlargement than did the treated cases (19 per cent *vs* 14 per cent). The difference is of borderline significance statistically and its meaning is difficult to evaluate, since, as in the case of cardiac enlargement, it may reflect the influence of anticoagulant therapy or differences in the groups prior to therapy, or both. Because of the complexities involved, discussion of this and other differences for the total period is reserved for the summary at the end of Chapter VI where deductions can be based on a coordinated view of all the data on signs, symptoms and laboratory findings. The percentage with hepatic enlargement among the control patients increased progressively with every decade of age between the fifth and the eighth decades inclusively, while the percentages among the treated patients rose very little after the fifth decade.

As presented in Table 51 and in Figure 40, the percentage of cases in the total sample and in the control and treated groups exhibiting moderate to severe hepatic enlargement was the same (4 per cent), but in the milder types, the control group was higher. The bulk of cases of hepatic enlargement were mild or moderate, a level which is particularly difficult to recognize and particularly prone to error in the estimation of its degree. Both the milder and the more severe types of enlargement increased with age (see Table 52, Appendix F Table 13, and Figure 41).

Comparison of the occurrence of hepatic enlargement by degree of severity, treatment group and period of illness is made in Table 53, Appendix F Table 14, and Figure 42. A modest decrease in the percentage of cases exhibiting this finding occurred after the first

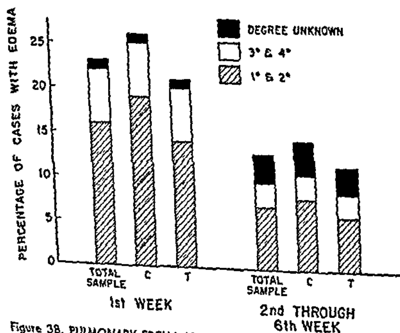


Figure 38. PULMONARY EDEMA BY PERIOD OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups showing maximum pulmonary edema of various degrees during the first week and from the second through the sixth week of observation.

TABLE 50

OCCURRENCE OF LIVER ENLARGEMENT: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Liver Enlargement of Any Degree during the Six-Week Period of Observation, by Age

Treatment Group	Percentage of Cases with Liver Enlargement[a]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
Total sample	16	*8*	9	15	19	22	*11*	—[b]
Control group	19	—[b]	6	16	23	33	—[b]	—[b]
Treated group	14	*6*	12	15	16	12	*14*	—[b]
	Number of Cases with Report on Liver Enlargement							
Total sample	1011	26	166	359	299	139	19	3
Control group	432	9	72	146	129	70	5	1
Treated group	579	17	94	213	170	69	14	2

Note: *Italics are used when percentages quoted have less than 50 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on the number of cases with a report on liver enlargement.

[b] Not computed since there were fewer than 10 cases in the sample.

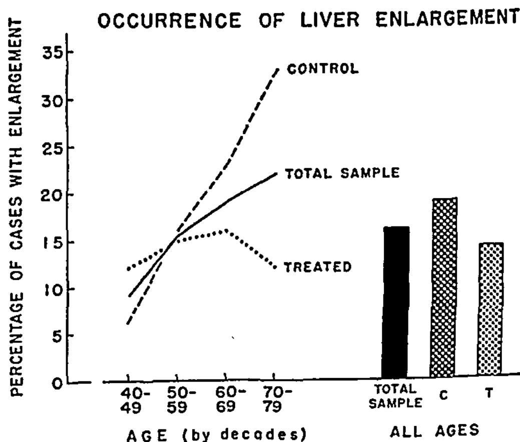


Figure 39. OCCURRENCE OF LIVER ENLARGEMENT: Percentage of cases in the total sample and in the control and treated groups showing liver enlargement of any degree during the six-week period of observation, by age.

week. This decrease was almost entirely due to a decrease in the percentage of cases exhibiting enlargement of one and two degrees. The [illegible] constant in the two periods. Since only maximum degrees of enlargement were reported, this does not mean that patients with hepatic engorgement retained such enlargement. It suggests that grossly enlarged livers did not shrink to the smaller size in so brief a period as a week.

For both the first and later weeks there was a considerably larger percentage of control than treated patients with enlarged livers.

TABLE 51

DEGREE OF LIVER ENLARGEMENT, BY TREATMENT GROUPS. Percentage of Cases in the Total Sample and in the Control and [illegible] Maximum Liver En- [illegible]

Maximum Degree of Liver Enlargement Reported at Any Time	Percentage of Cases*		
	Total Sample	Control Group	Treated Group
None	84	81	86
Mild to moderate			
One degree	5	7	3
Two degrees	6	7	6
Total mild to moderate	11	14	9
Moderate to severe.			
Three degrees	3	3	3
Four degrees	1	1	1
Total moderate to severe	4	4	4
Degree unknown	1	1	1
Total with liver enlargement	16	19	14
	Number of Cases with Report on Liver Enlargement		
Total cases	1011	432	579

* Based on number of cases with a report on liver enlargement.

Differences in both periods were due to hepatic enlargement of the lesser degrees and [illegible] centage in both groups during both periods.

Peripheral Edema

Peripheral edema, also an evidence of right heart failure, was recognized in 10 per cent of the 1018 cases in the total series with a report on this subject. No significant difference was found in the percentage of patients presenting this finding in the control and treated groups and differences by decades of age were minor (see Table 54, Appendix F Table 13, and Figure 43). However, there was a definite increase with age in the percentage of patients in each category over the age of sixty years who exhibited dependent edema, so that the incidence during the eighth decade was roughly two and one-half times that during the fifth decade. As Table 55, Appendix F Table 13, and Figure 44 indicate, in the majority of instances, this peripheral edema was of mild or mild to moderate severity *only*. Edema of lesser degrees increased steadily through each decade of age from the fifth on (see Table 56, Appendix F Table 13 and Figure 45). More severe dependent edema did not increase in frequency until the sixth decade and then the increase was only to a modest extent.

Data by periods given in Table 57, Appendix F Table 14, and Figure 46 show no great or statistically significant difference between the total sample and the control and treated groups for either period of study. There was, however, a decrease in the frequency of dependent edema during the period following the first week. This decrease was due largely, though not entirely, to a decrease in the percentage of cases exhibiting mild to moderate edema. There was also a smaller decrease in the percentages of cases exhibiting moderate to severe dependent edema after the first week.

TABLE 50

OCCURRENCE OF LIVER ENLARGEMENT: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Liver Enlargement of Any Degree during the Six-Week Period of Observation, by Age

Treatment Group	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
	Percentage of Cases with Liver Enlargement[a]							
Total sample	16	*8*	9	15	19	22	*11*	—[b]
Control group	19	—[b]	6	16	23	33	—[b]	—[b]
Treated group	14	*6*	12	15	16	12	*14*	—[b]
	Number of Cases with Report on Liver Enlargement							
Total sample	1011	26	166	359	299	139	19	3
Control group	432	9	72	146	129	70	5	1
Treated group	579	17	94	213	170	69	14	2

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on the number of cases with a report on liver enlargement.

[b] Not computed since there were fewer than 10 cases in the sample.

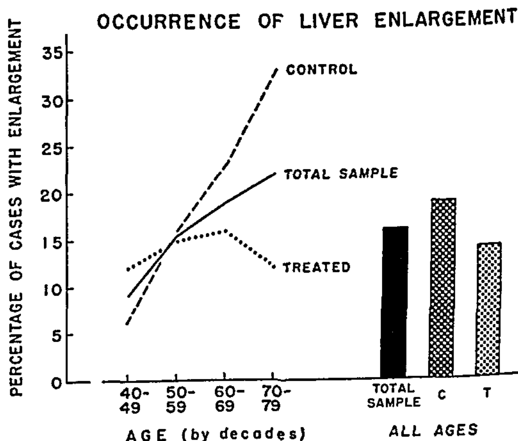


Figure 39. OCCURRENCE OF LIVER ENLARGEMENT: Percentage of cases in the total sample and in the control and treated groups showing liver enlargement of any degree during the six-week period of observation, by age.

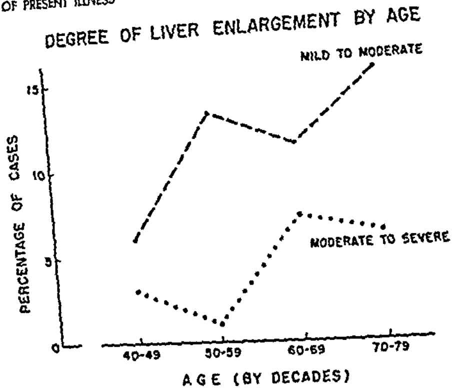


Figure 41. DEGREE OF LIVER ENLARGEMENT BY AGE: Percentage of cases in the total sample showing maximum liver enlargement of various degrees during the six-week period of observation, by age.

TABLE 53

[illegible]

Sixth Week of Observation

Maximum Degree of Liver Enlargement Reported at Any Time	Percentage of Cases*					
	1st Week			2nd through 6th Week		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
None. ...	87	84	88	90	89	91
Mild to moderate (1st or 2nd degree)	9	12	8	6	7	5
Moderate to severe (3rd or 4th degree)	3	3	3	3	2	3
Degree unknown	1	1	1	1	2	1
Total with report on liver enlargement	100	100	100	100	100	100
	Number of Cases with Report on Liver Enlargement					
Total cases at beginning of the period	1006	428	578	919	386	533

* Based on number of cases with a report on liver enlargement.

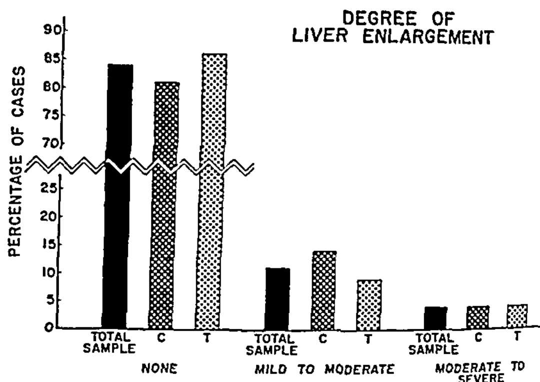


Figure 40. DEGREE OF LIVER ENLARGEMENT: Percentage of cases in the total sample and in the control and treated groups showing maximum liver enlargement of various degrees during the six-week period of observation.

TABLE 52

DEGREE OF LIVER ENLARGEMENT, BY AGE: Percentage of Cases in the Total Sample Showing Maximum Liver Enlargement of Various Degrees during the Six-Week Period of Observation, by Age

Maximum Degree of Liver Enlargement Reported at Any Time	Percentage of Cases[a]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
None	84	*92*	91	85	81	78	*89*	—[b]
Mild to moderate (1st or 2nd degree)	11	*8*	6	13	11	15	*6*	—[b]
Moderate to severe (3rd or 4th degree)	4	—	3	1	7	6	*5*	—[b]
Degree unknown	1	—	—	1	1	1	—	—[b]
Total with report on liver enlargement	100	*100*	100	100	100	100	*100*	—[b]
	Number of Cases with Report on Liver Enlargement							
Total cases	1011	26	166	359	299	139	19	3

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable*

[a] Based on number of cases with a report on liver enlargement.

[b] Not computed since there were less than 10 cases in the sample.

Abnormal Rhythms and Conduction Defects

The presence of abnormal rhythms constitute still another manifestation of the impaired heart action resulting from myocardial infarction. A report on the presence or absence of an observed abnormal rhythm or conduction defect during the six-week period covered by this study was available for all but 16 patients in this study. Because of the very great difference in the nature of the rhythms reported and in their prognostic significance and because of the extreme variation in the care with which they were studied electrocardiographically and clinically, the summarized figures must be considered understatements and approximations only.

The following facts are demonstrated in Table 58 (based on Appendix F, Table 15) and in Figure 47. During the first week of the illness, 36 per cent of those for whom a report on the presence or absence of arrhythmias was received, exhibited one or another type of cardiac arrhythmia or conduction defect. The percentages reported for the control and treated groups were almost identical, being 37 and 35 per cent respectively. During the second through the sixth week of observation, both percentages fell off by about one-quarter, being respectively 29 per cent and 25 per cent for later weeks. There was a slightly greater drop in the treated group but the resulting difference in later weeks was not statistically significant.

Further reference to Table 58 and Figure 47 indicates that the occurrence of these abnormalities increased in general with each decade of age. However, during both periods and in both treatment groups, and in consequence in the total sample, the percentage of cases exhibiting these abnormalities remained essentially constant during the sixth and seventh decades. In the control group this

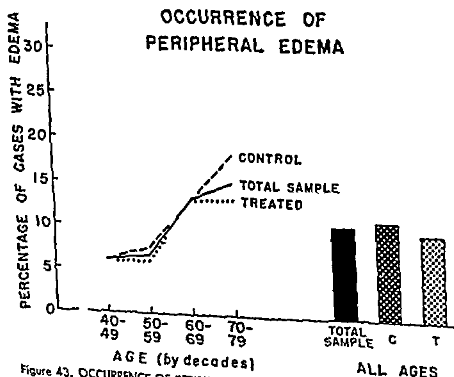


Figure 43. OCCURRENCE OF PERIPHERAL EDEMA: Percentage of cases in the total sample and in the control and treated groups showing peripheral edema of any degree during the six-week period of observation, by age.

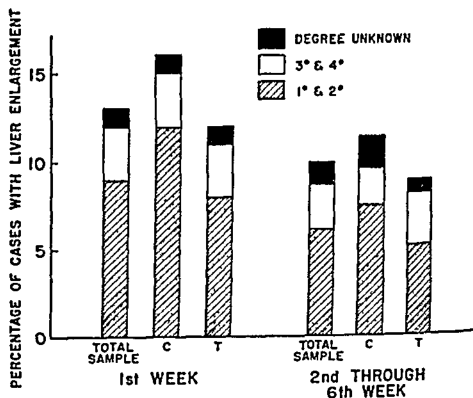


Figure 42. LIVER ENLARGEMENT BY PERIOD OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups showing maximum liver enlargement of various degrees during the first week and from the second through the sixth week of observation.

TABLE 54

OCCURRENCE OF PERIPHERAL EDEMA: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Peripheral Edema of Any Degree during the Six-Week Period of Observation, by Age

Treatment Group	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
	Percentage of Cases with Peripheral Edema[a]							
Total sample	10	*12*	6	7	13	15	*32*	—[b]
Control group	11	—[b]	6	7	13	18	—[b]	—[b]
Treated group	10	*6*	6	6	13	13	*36*	—[b]
	Number of Cases with Report on Peripheral Edema							
Total sample	1018	26	166	367	300	137	19	3
Control group	437	9	72	151	131	68	5	1
Treated group	581	17	94	216	169	69	14	2

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on the number of cases with a report on peripheral edema.

[b] Not computed since there were fewer than 10 cases in the sample.

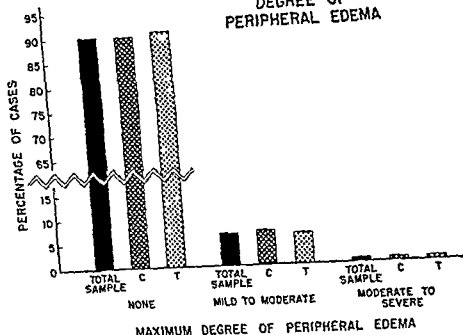


Figure 44. DEGREE OF PERIPHERAL EDEMA: Percentage of cases in the total sample and in the control and treated groups showing maximum peripheral edema of various degrees during the six-week period of observation.

TABLE 56

DEGREE OF PERIPHERAL EDEMA, BY AGE: Percentage of Cases in the Total Sample Showing Maximum Peripheral Edema of Various Degrees during the Six-Week Period of Observation, by Age

Maximum Degree of Peripheral Edema Reported at Any Time	Percentage of Cases[a]							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
None	90	*88*	94	93	87	85	*68*	—[b]
Mild to moderate (1st or 2nd degree)	8	*8*	4	6	9	11	*26*	—[b]
Moderate to severe (3rd or 4th degree)	1	*4*	1	1	2	3	—	—[b]
Degree unknown	1	—	1	—	2	1	*6*	—[b]
Total with report on peripheral edema	100	*100*	100	100	100	100	*100*	100
	Number of Cases with Report on Peripheral Edema							
Total cases	1018	26	166	367	300	137	19	3

Note. *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on number of cases with a report on peripheral edema.

[b] Not computed since there were less than 10 cases in the sample.

levelling was evident also in the fifth decade. It is unlikely that it is due entirely to chance since the numbers of cases in these samples are not insignificant.

Individual arrhythmias described with any great frequency were few in number. Those occurring during the first week of the illness with a frequency in the total sample of more than two per cent included only premature contractions, ectopic beats or extrasystoles not specified as premature, auricular fibrillation and bundle branch block (right or left). Heart block of any type, including bundle branch block was reported in 103 cases in the entire sample during this week and ventricular tachycardia in 13 cases (7 control, 6 treated) including transient types. Auricular flutter was reported in only 10 cases and paroxysmal tachycardia in only 8 cases. Specific arrhythmias, as reported by week of illness and treatment group, are shown in Appendix F, Table 16. In Figure 48, the occurrence of the more common arrhythmias is presented by periods. The second through the sixth week showed in most respects a substantial improvement over the first week. Differences between treatment groups, as shown in Appendix F, Table 16, were small and probably without medical significance.

TABLE 55

DEGREE OF PERIPHERAL EDEMA, BY TREATMENT GROUPS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Peripheral Edema of Various Degrees during the Six-Week Period of Observation

Maximum Degree of Peripheral Edema Reported at Any Time	Percentage of Cases[a]		
	Total Sample	Control Group	Treated Group
None	90	89	90
Mild to moderate:			
One degree	5	5	5
Two degrees	3	4	3
Total mild to moderate	8	9	8
Moderate to severe:			
Three degrees	1	1	1
Four degrees	—[b]	—[b]	—
Total moderate to severe	1	1	1
Degree unknown	1	1	1
Total with edema	10	11	10
	Number of Cases with Report on Edema		
Total cases	1018	437	581

[a] Based on number of cases with a report on peripheral edema.
[b] Less than .5 of 1 percent.

According to Mintz and Katz,[152] cardiac arrhythmias occur in somewhat more than 15 per cent of all patients suffering a myocardial infarction. In a review of the literature by these authors, the incidence of cardiac arrhythmias following myocardial infarction ranged from 9 to 27 per cent, with an average of 18 per cent. In their own series of 572 cases of recent myocardial infarction, the incidence of cardiac arrhythmias, excluding occasional premature systoles, sinus tachycardia or intraventricular block, was 16 per cent.

In the series of Pearson[153] in which older patients predominated (average age was 64.5 years) and the severity of the illness was greater than average, 25 per cent of the cases showed arrhythmias when cases with bundle branch block and sporadic ectopic beats were excluded.

According to the literature, which differs markedly on this point, the most commonly observed arrhythmias following myocardial infarction are premature ventricular systoles, auricular fibrillation, heart block and paroxysmal tachycardia. In the series reported by Mintz and Katz,[152] the most frequently observed arrhythmias were first degree heart block, auricular fibrillation, second degree heart block and ventricular tachycardia, with occasional premature systoles, sinus tachycardia and intraventricular block being excluded from their analysis.

The prognostic implications of the various types of cardiac arrhythmias will be discussed in Chapters VIII and XI.

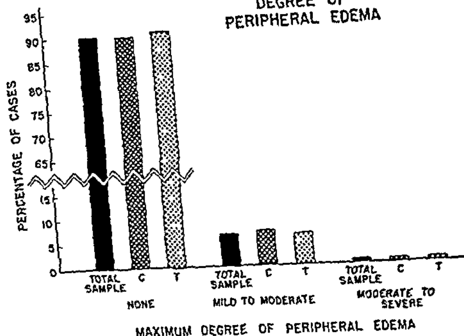


Figure 44. DEGREE OF PERIPHERAL EDEMA: Percentage of cases in the total sample and in the control and treated groups showing maximum peripheral edema of various degrees during the six-week period of observation.

TABLE 56

DEGREE OF PERIPHERAL EDEMA, BY AGE: Percentage of Cases in the Total Sample Showing Maximum Peripheral Edema of Various Degrees during the Six-Week Period of Observation, by Age

Maximum Degree of Peripheral Edema Reported at Any Time	Percentage of Cases[a]							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
None	90	88	94	93	87	85	*68*	—[b]
Mild to moderate (1st or 2nd degree)	8	8	4	6	9	11	*26*	—[b]
Moderate to severe (3rd or 4th degree)	1	*4*	1	1	2	3	—	—[b]
Degree unknown	1	—	1	—	2	1	*6*	—[b]
Total with report on peripheral edema	100	*100*	100	100	100	100	*100*	*100*
	Number of Cases with Report on Peripheral Edema							
Total cases	1018	26	166	367	300	137	19	3

Note. *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on number of cases with a report on peripheral edema.

[b] Not computed since there were less than 10 cases in the sample.

DEGREE OF PERIPHERAL EDEMA BY AGE

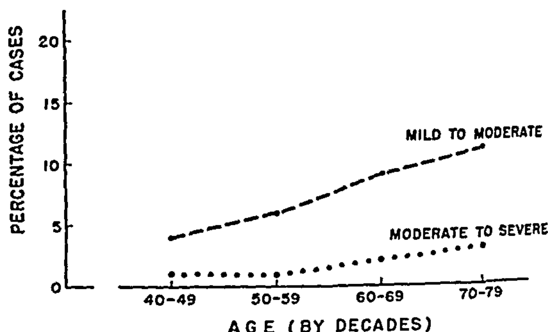


Figure 45. DEGREE OF PERIPHERAL EDEMA BY AGE: *Percentage of cases in the total sample showing maximum peripheral edema of various degrees during the six-week period of observation, by age.*

TABLE 57

DEGREE OF PERIPHERAL EDEMA, BY PERIOD OF ILLNESS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Peripheral Edema of Various Degrees during the First Week and from the Second through the Sixth Week of Observation

Maximum Degree of Peripheral Edema Reported at Any Time	Percentage of Cases[a]					
	1st Week			2nd through 6th Week		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
None	92	92	92	95	94	96
Mild to moderate (1st or 2nd degree)	6	6	6	3	3	2
Moderate to severe (3rd or 4th degree)	1	1	1	—[b]	1	—[b]
Degree unknown	1	1	1	2	2	2
Total with report on peripheral edema	100	100	100	100	100	100
	Number of Cases with Report on Peripheral Edema					
Total cases at beginning of the period	1018	438	580	940	405	535

[a] Based on number of cases with a report on peripheral edema.

[b] Five-tenths of 1 per cent, or less.

Gallop Rhythm

During the first week of the illness, a gallop rhythm was reported in 6 per cent of the 1015 cases for which there was a report on cardiac rhythms. This rhythm was identified in 7 per cent of the control cases and 6 per cent of the treated cases during the first week. Among those with a report on cardiac rhythms after the first week, a gallop rhythm was identified in later weeks in 3 per cent of the total sample, 4 per cent of the control group and 3 per cent of the treated group. These data are recognized as being subject to considerable error in recognition and in interpretation.

Adams-Stokes Attacks

Adams-Stokes attacks were reported as occurring in only 4 instances in the total sample during the first week of the illness and in only 1 instance in the total sample during the second through the sixth week of the illness.

Maximum Pulse Rate

Since pulse rates give important information as to the patient's progress, the participating hospitals were asked to report the maximum daily pulse rate for each patient through the entire six-week period of observation. In a relatively small number of cases the period of observation was short or the reporting of the pulse rate was infrequent so that only one or two maximum pulse readings were reported for the first week (62 cases) and for the second through the sixth week (19 cases). In some instances the pulse rate was reported as being "above" a certain

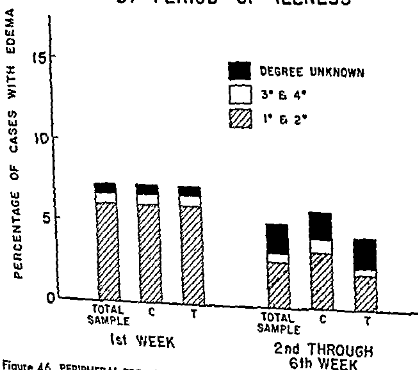


Figure 46. PERIPHERAL EDEMA BY PERIOD OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups showing maximum peripheral edema of various degrees during the first week and from the second through the sixth week of observation.

figure and, in those instances, the figure quoted was used in the tabulations. Some data on the daily maximum pulse rate during the first week of illness were provided for 951 patients, and for the second through the sixth week, for 949 patients.

The actual level at which an accelerated pulse rate is termed "tachycardia" varies somewhat in the literature, but a rate of 100 beats per minute is, perhaps, most widely accepted and has been adopted as a critical level in making the calculations and tabulations presented here. That 100 beats per minute approximates a critical level appears to be borne out by the significant contrast between the percentage of patients among "cases dying" and that for "cases surviving" who exhibited maximum pulse rates above or below 100.

In the following discussion, the maximum pulse rates are compared among patients in the control and treated groups, not only by period of illness, but also by whether the patient died or survived the six-week period of observation. Presentations are based in each instance on the highest readings reported during the period.

The mean values for the maximum pulse rates within each of these subcategories are shown in Table 59 and, graphically, in Figure 49. These data show that the mean maximum pulse rates differed only slightly between the control and treated groups during either period of observation, irrespective of

TABLE 58

ARRHYTHMIAS, ANY TYPE: *Percentage of Cases in the Total Sample and in the* Control and Treated Groups for Whom Any Type of Abnormal Rhythm Was Reported for the First Week and from the Second through the Sixth Week of Observation

Period of Illness and Treatment Group	Percentage of Cases[a] with Any Arrhythmias[b]							
	All Ages	*Under 40*	*40–49*	*50–59*	*60–69*	*70–79*	*80–89*	*Age Unknown*
First week:								
Total sample	36	*42*	27	34	33	51	*78*	—[c]
Control group	37	—[c]	34	32	35	52	—[c]	—[c]
Treated group	35	*35*	23	35	32	49	*85*	—[c]
Second through sixth week:								
Total sample	26	*29*	21	22	27	39	*64*	—[c]
Control group	29	—[c]	21	26	26	47	—[c]	—[c]
Treated group	25	*27*	21	20	28	32	—[c]	—[c]
	Number of Cases with Report on Arrhythmias during Period							
First week:								
Total sample	1015	26	164	365	301	138	18	3
Control group	433	9	71	148	132	67	5	1
Treated group	582	17	93	217	169	71	13	2
Second through sixth week:								
Total sample	921	24	156	344	267	116	11	3
Control group	392	9	66	145	115	53	3	1
Treated group	529	15	90	199	152	63	8	2

Note: *Italics are used when percentages quoted have less than 50 cases as a base since chance factors render such rates particularly unstable.*

[a] [illegible] report on arrhythmias during period.

[b] [illegible] ally [illegible]

[c] Not computed since there were less than 10 cases in the sample.

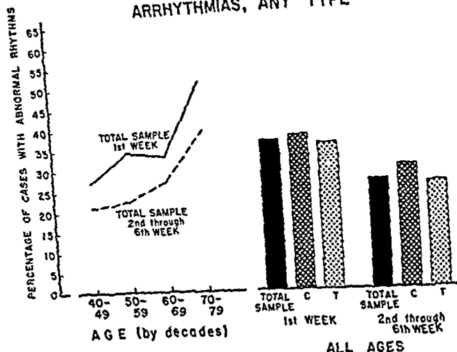


Figure 47. ARRHYTHMIAS, ANY TYPE: Percentage of cases in the total sample and in the control and treated groups reported to have shown any type of arrhythmia during the first week and from the second through the sixth week of observation, and similar percentages for the total sample only, by age.

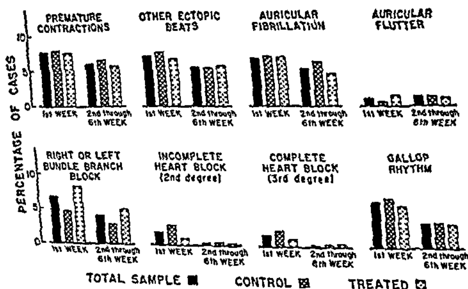


Figure 48. SELECTED ARRHYTHMIAS· Percentage of cases in the total sample and in the control and treated groups exhibiting selected arrhythmias during the first week and from the second through the sixth week of observation.

whether all cases were compared, or just those cases dying or surviving. The greatest difference in this respect occurred when cases dying in the control and treated groups were compared for later weeks, the difference in means in this instance being only 8 beats per minute.

Comparison of the means of the maximum pulse rates in each outcome category for the first week of illness with those for later weeks shows, almost without exception, consistent, but remarkably slight decreases during the latter period. In no instance did the decrease in means exceed 6 beats per minute. This lack of difference is due, no doubt, in part to the use of maximums. During the period from the second through the sixth week there was, of course, much more opportunity to observe a high rate than during the first week and one high observation was sufficient to establish a high maximum.

TABLE 59

MEANS OF MAXIMUM PULSE RATES: Means of Maximum Pulse Rates Reported for All Cases in the Total Sample and in the Control and Treated Groups, by Period of Illness and Survival Status

Period of Illness and Treatment Group	Mean of Maximum Pulse Rates[a]		
	All Cases	Cases Dying Within Six Weeks	Cases Surviving Six-Week Period
First week:			
Total sample	108	118	105
Control group	108	120	104
Treated group	107	117	106
Second through sixth week:			
Total sample	102[b]	116[b]	100
Control group	103[b]	120[b]	100
Treated group	101[b]	112[b]	100

[a] Computed from maximum rate reported for period for each case for which one or more pulse rates were reported for period in question. For number of cases involved in each mean, see Table 60.

[b] Means for the second through the sixth week necessarily exclude those in the first-week group who failed to survive to the beginning of the second week.

The most significant finding in this respect was that among survivors the mean of the maximum pulse rates was only 105 beats per minute during the first week, and 100 beats per minute during the later weeks, whereas, among the patients who died, the mean of the maximum pulse rates was 118 beats per minute during the first week and among those surviving the first week, dying later, 116 beats during subsequent weeks. These contrasts by survival status occurred in both the control and treated groups but were slightly greater in the control group. *A high pulse rate is clearly an unfavorable prognostic sign.*

Table 60 and Figure 50 approach the same data in terms of the percentage of cases with maximum pulse rates of 100 beats per minute or more. Pulses at this level were observed at some time during the first week in 62 per cent of the patients studied. The major contrast was that between patients who subsequently died and those who survived the period of observation, 83 per cent of those dying showing such maximum rates as contrasted with 58 per cent of those surviving. For those who lived until the second week, the proportion showing maximum tachycardia at this level fell to approximately 49 per cent during later weeks. Again, a considerably greater percentage of patients who died during this second period exhibited tachycardia at this level than did patients who survived this period (77 per cent compared with 45 per cent).

When the control and treated groups were examined separately, this same pattern of relationships by period and survival status was, with one exception, apparent in each. Differences between the control and treated groups in comparable subclasses were small or absent except in the case of control cases dying. Only this subgroup failed to show a drop in the proportion of cases with maximum rates of 100 or more in later weeks. The contrast in this respect with the treated group cases dying may reflect a reduction in thromboembolic complications prior to death in treated group cases who nevertheless eventually died from other causes. The fact that

treated survivors did not show an equally superior pulse record in comparison with control survivors could well be due to the addition to the treated survivor group of severe cases of a type that in the control group would not have survived beyond the first week without anticoagulants and hence in the control group would appear in the "cases dying" column. The reduction in mortality associated with anticoagulants (see Chapter XI) unavoidably complicates statistical comparisons involving statistical subdivisions by survival status.

The same factor also renders difficult definitive evaluation of the comparative records from the second through the sixth week for the total control and treated groups since cases dying in the first week do not appear in the base from which rates for the later period are computed. *Thus, in this and all comparisons for later weeks, the treated group is given an unfair handicap since it includes, by reason of the therapy already given, types of cases that in the control group probably would not have survived to be included at all.* Probably this factor helps to explain why the differential between the total control and treated groups in maximum pulse rates, though increased during later weeks in favor of the treated group, was not sufficient in either period to be statistically significant. Maximum pulse rates also are a rather insensitive index since a single high reading can put a case that fared relatively well in the same classification with a continuously severe, moribund case. Average pulse rates in later weeks, if computed, might well have been more favorable to the treated group.

The percentage of cases with maximum pulse rates at various specific levels is tabulated by periods in Appendix F, Tables 17 and 18 and considered graphically for the

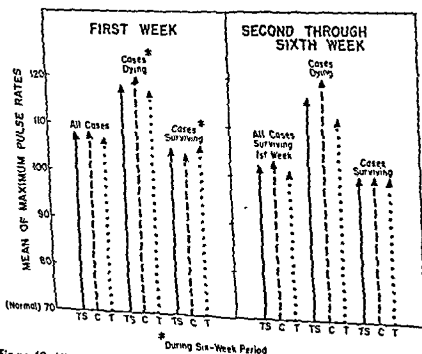


Figure 49. MEANS OF MAXIMUM PULSE RATES: Means of maximum pulse rates reported for all cases, cases dying within six weeks and cases surviving in the total sample and in the control and treated groups, by period of illness.

first week in Figure 51 and for the second through the sixth week in Figure 52. Both figures show clearly the difference in maximum pulse for those dying and those surviving and *confirm the unfavorable prognosis associated with high pulse rates*. Inspection of the changing ratio in Appendix F, Table 17 of those dying to those surviving suggests that 120 beats per minute is the critical level at which the prognosis becomes highly unfavorable. Levels from the second through the sixth week are in general lower, but the difference by survival status remains marked, especially in the higher pulse ranges. Cases dying during the first week are, of course, not included in the base for the second through the sixth week, so that the data for later weeks relate as a whole to a less acute type of case.

TABLE 60

PULSE RATES OF 100 OR MORE: Percentage of Cases with Maximum Pulse Rates of One Hundred Beats per Minute or More Reported for All Cases in the Total Sample and in the Control and Treated Groups, by Period of Illness and Survival Status

Period of Illness and Treatment Group	Percentage of Cases with Maximum Pulse Rates of 100 Beats per Minute or More[a]		
	All Cases	Cases Dying Within Six Weeks	Cases Surviving Six-Week Period
First week:			
Total sample	62	83	58
Control group	62	86	56
Treated group	62	79	59
Second through sixth week:			
Total sample	49[b]	77[b]	45
Control group	50[b]	87[b]	44
Treated group	47[b]	65[b]	46
	Number of Cases with Report on Pulse Rate in Period		
First week:			
Total sample	951	178	773
Control group	403	88	315
Treated group	548	90	458
Second through sixth week:			
Total sample	949	113	836
Control group	405	61	344
Treated group	544	52	492

[a] Based on number of cases with a report on pulse rate for the period in question.

[b] Cases dying before the beginning of the second week are excluded from the base of percentages for the second through the sixth week.

When the distribution of maximum pulse rates for the control and treated groups is compared, as is possible from Appendix F, Table 18, it is clear that the relative position of the two groups follows the same pattern previously commented on for the percentage of cases with maximum rates of 100 beats or more per minute. Again rates clearly favorable to anticoagulants appeared during later weeks only among patients dying before the end of the period. The probable explanation is complex and the same as previously indicated.

While the extent of bradycardia is also of interest, these figures should not be used for deductions about slow rates since only maximum rates were selected for study. Bradycardia was present on some days in a number of patients having maximum rates at higher levels but is not revealed by the present method of analysis.

Acute coronary occlusion with myocardial infarction is commonly accompanied by an elevated pulse rate. Such an elevation often persists for variable periods following the acute attack. Both Levine and Brown[115] and Master, Dack and Jaffe[135] have stressed the fact that sinus tachycardia is a grave sign in acute myocardial infarction. Detailed comparisons of other studies with the present one are difficult because of differences in counting and reporting procedures.

Yater et al.[265] reported on the pulse rate in 388 of their 400 patients who survived myocardial infarction. The pulse rate exceeded 100 beats per minute in 23.5 per cent. In contrast, the pulse rate did not exceed 60 beats per minute in 16.5 per cent. Among the patients who died, records of the pulse rate were obtained in only about 70 patients and tachycardia was reported in only 8 in-

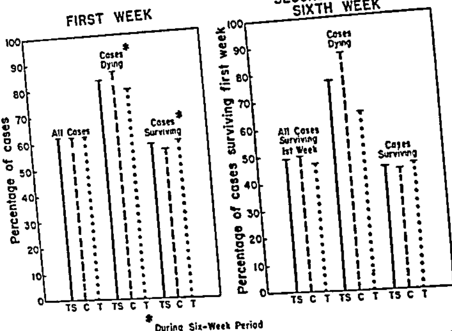


Figure 50. MAXIMUM PULSE RATES OF 100 OR MORE: Percentage of cases with maximum pulse rates of 100 beats per minute or more reported for all cases, cases dying, and cases surviving in the total sample and in the control and treated groups, by period of illness.

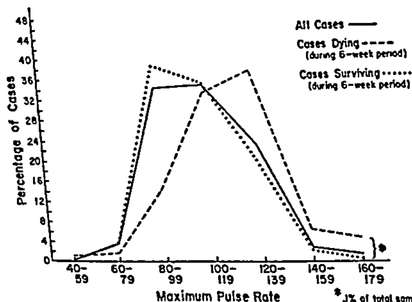


Figure 51. MAXIMUM PULSE, FIRST WEEK: Percentage of all cases, cases dying within six weeks and cases surviving in the total sample with a maximum pulse rate at various levels during the first week of observation.

first week in Figure 51 and for the second through the sixth week in Figure 52. Both figures show clearly the difference in maximum pulse for those dying and those surviving and *confirm the unfavorable prognosis associated with high pulse rates.* Inspection of the changing ratio in Appendix F, Table 17 of those dying to those surviving suggests that 120 beats per minute is the critical level at which the prognosis becomes highly unfavorable. Levels from the second through the sixth week are in general lower, but the difference by survival status remains marked, especially in the higher pulse ranges. Cases dying during the first week are, of course, not included in the base for the second through the sixth week, so that the data for later weeks relate as a whole to a less acute type of case.

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PULSE RATES OF 100 OR MORE: Percentage of Cases with Maximum Pulse Rates of One Hundred Beats per Minute or More Reported for All Cases in the Total Sample and in the Control and Treated Groups, by Period of Illness and Survival Status

Period of Illness and Treatment Group	Percentage of Cases with Maximum Pulse Rates of 100 Beats per Minute or More[a]		
	All Cases	Cases Dying Within Six Weeks	Cases Surviving Six-Week Period
First week:			
Total sample	62	83	58
Control group	62	86	56
Treated group	62	79	59
Second through sixth week:			
Total sample	49[b]	77[b]	45
Control group	50[b]	87[b]	44
Treated group	47[b]	65[b]	46
	Number of Cases with Report on Pulse Rate in Period		
First week:			
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Second through sixth week:			
Total sample	949	113	836
Control group	405	61	344
Treated group	544	52	492

[a] Based on number of cases with a report on pulse rate for the period in question.

[b] Cases dying before the beginning of the second week are excluded from the base of percentages for the second through the sixth week.

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nostic sign in both sexes since the mortality in patients exhibiting it was 50.6 per cent for males and 67.6 per cent for females. Sinus tachycardia was an especially grave sign when it occurred in the presence of congestive heart failure.

Katz, Mills and Cisneros[164] observed that the mortality rate during the first two months following myocardial infarction was definitely greater in the presence of sinus tachycardia than in its absence. Patients with tachycardia who survived this period exhibited thereafter as favorable a prognosis as did the entire group of patients observed.

Tredway[222] found that the average pulse rate at the time of hospital admission following acute myocardial infarction was materially higher among the subsequently fatal cases than among those patients who survived the attack The average pulse rate upon admission was 99 beats per minute (range of 48 to 150) for the fatal cases and 87 beats per minute (range 41 to 125) for the patients who survived.

Maximum Temperature

Since temperature levels also provide important evidence of the patient's progress, reports of the maximum daily temperature for each patient through the entire six-week period of observation were requested. Reporting on this topic was relatively complete for the period of hospitalization, but for patients admitted late to the hospital or dying early, the total number of daily temperature reports was necessarily low (occasionally only one or two days). Data on maximum daily temperatures during hospitalization were available for 948 patients for the first week of the illness and for 943 patients for the second through the sixth week. In the tabulation of temperatures for analysis, all readings were expressed in degrees Fahrenheit. When oral temperatures were reported, they were converted to their approximate rectal equivalent by the routine addition of a degree.

From the maximum daily temperatures reported, the highest reading in the first week and the highest from the second through the sixth week were selected for each patient. The analysis compares patients in the control and treated groups with respect to these maximums by periods and, within each group and period, compares those patients dying and those surviving the six-week period.

The mean values for the maximum temperatures reported in each of these subcategories appear in Table 61 and, graphically, in Figure 53. These data show that, when comparable categories are compared, the mean maximum temperatures differed only slightly between the control and treated groups. The greatest difference between treatment groups is noted when cases dying

TABLE 61

MEANS OF [illegible]

Period of Illness and Treatment Group	Mean of Maximum Rectal Temperatures[a] (Fahrenheit)		
	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period
First Week:			
Total sample	101.7°	102.4°	101.5°
Control group	101.8°	102.6°	101.5°
Treated group	101.6°	102.3°	101.4°
Second through sixth week:			
Total sample	100.9°[b]	102.2°[b]	100.8°
Control group	101.0°[b]	102.4°[b]	100.8°
Treated group	100.9°[b]	101.9°[b]	100.7°

[a] Computed from maximum temperature reported for period for each case for which one or more temperatures were reported for period in question. For number of cases involved in each mean, see Table 62

[b] Means for the second through the sixth week necessarily exclude those in the first-week group who failed to survive to the beginning of the second week.

stances, bradycardia, in one. The relative youth of the group analyzed and the fact that the findings cover only an initial observation period may account for these relatively low rates.

In Bean's series[14] of 300 patients with coronary occlusion and myocardial infarction who came to autopsy, abnormal pulse rates as a symptom (sic) of the acute attack were reported as follows: Tachycardia, defined as a rate over 108 beats per minute, occurred in 42 per cent of 102 patients experiencing a first attack and in 48 per cent of 67 patients experiencing a second attack. Bradycardia, defined as a rate less than 60 beats per minute, occurred in 16 per cent of 102 patients experiencing a first attack and in 15 per cent of 67 patients experiencing a second attack.

Chambers[41] found that the average pulse rate in fatal cases was 115 beats per minute upon admission to the hospital and that this rapid pulse usually persisted until death. Tachycardia was present in every fatal case, but one. Among patients surviving the observed attack, the pulse averaged only 100 beats per minute upon admission and returned to normal after a period which averaged 8 days.

Mintz and Katz[133] observed that, of their 572 patients, 116, or 20.3 per cent, exhibited a sinus tachycardia (ventricular rate over 100) at the time the first electrocardiogram was taken. Of these 116 patients, 57 per cent died as compared with 22 per cent of their entire series. In the experience of Mintz and Katz, sinus tachycardia was a grave prog-

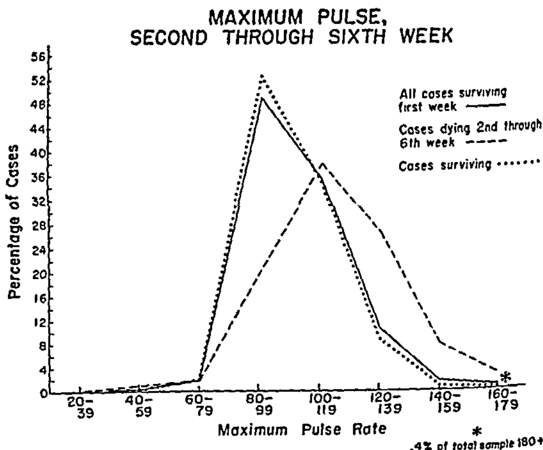


Figure 52. MAXIMUM PULSE, SECOND THROUGH SIXTH WEEK: Percentage of cases with a maximum pulse rate at various levels during the second through the sixth week among all cases in the total sample surviving the first week, among cases dying during the second through the sixth week, and among cases surviving these weeks.

period were the differences between the total control and total treated group statistically significant.

The number and percentage of cases with maximum rectal temperatures at various specific levels are tabulated in Appendix F, Tables 19 and 20 and are presented graphically for the first week in Figure 54 and for the second through the sixth week in Figure 55. *Both figures show clearly that patients who died tended to have higher maximum temperatures during the period in question than did those patients who survived.* Levels of maximum temperature for later weeks were in general lower than those during the first week, but the difference by survival status remained marked, especially in the higher temperature ranges. As with maximum pulse rates, cases dying during the first week are not included in the base for the second through the sixth week.

The unfavorable prognosis associated with a high temperature during the first week is clearly evident if Appendix F, Table 19 is read horizontally, the number of cases dying within six weeks being computed as a percentage of the total cases in a given temperature category. When this table is read in this manner, it is found that 46 per cent of the control group and 40 per cent of the treated group with temperature maximums of 103 degrees or more in the first week died within six weeks, whereas among those with corresponding maximums of 101.0–102.9 degrees, only 22 per cent of the control group and 15 per cent of the treated group died (see Figure 56). Below 101 degrees, the corresponding percentages were only 7 and 10 per cent respectively.[b]

Similar percentages shown in Figure 57 and based on Appendix F, Table 20 reporting counts for the second through the sixth week indicate that *a similarly grave prognosis is associated with temperatures of 103 degrees or* [illegible] maximum temperatures of 103 degrees or more sometime during the second through the sixth week were 60 per cent dying within six weeks in the control group as compared with 31 per cent in the treated group. For patients with maximums between 101.0 and 102.9 degrees, corresponding percentages were 17 and 12 per cent respectively and below 101 degrees, 7 and 6 per cent.

TABLE 62

[illegible] Cases in the Total Sample and in the Control and Treated Groups, by Period of Illness and Survival Status

Period of Illness and Treatment Group	Percentage of Cases with Maximum Rectal Temperatures of 100°F or More[a]		
	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period
First week:			
Total sample	91	97	90
Control group	92	97	91
Treated group	90	98	89
Second through sixth week:			
Total sample	82[b]	88[b]	81
Control group	80[b]	88[b]	78
Treated group	83[b]	89[b]	82
	Number of Cases with Report on Temperature for Period		
First week:			
Total sample	948	180	768
Control group	406	90	316
Treated group	542	90	452
Second through sixth week:			
Total sample	943	112	831
Control group	403	60	343
Treated group	540	52	488

[a] Based on number of cases with a report on temperature for the period in question

[b] Cases dying before the beginning of the second week are excluded from the base of percentages for the second through the sixth week.

[b] Percentages cited are based on counts corrected for exceptions in treatment in the manner described in Appendix B. Those interested in uncorrected percentages can readily compute them from the counts in Appendix F, Table 19.

in the control and treated groups during the period of the second through the sixth week are compared, but the difference in means even in this instance is only one-half of a degree Fahrenheit.

Comparison of the means for survivors in each group during the first week of illness with corresponding values for the same group for later weeks shows a slight reduction in maximum temperature during the latter period, irrespective of treatment status. Those dying within six weeks showed, however, little improvement in maximum level after the first week and even this difference may be spurious since, by the later weeks, some members of this group in the first week had already died.

As might well be anticipated, 91 per cent of all patients in this series exhibited an elevation of temperature to 100 degrees Fahrenheit or more during the first week of illness (see Table 62), while 82 per cent of those who survived into the period of the second through the sixth week exhibited a similar elevation. Irrespective of the period of observation, or of the treatment status of the patient, a noticeably higher percentage of patients who died during the six-week period of observation than of patients who survived exhibited an elevation of temperature above 100 degrees Fahrenheit. The percentages during the first week were 97 per cent for cases dying and 90 per cent for cases surviving; during later weeks the percentages were 88 per cent for cases dying from the second through the sixth week and 81 per cent for cases surviving.

When the percentage of cases exhibiting a maximum rectal temperature of 100 degrees Fahrenheit or greater during the first and during later weeks of the illness is compared by subcategories, one finds a definite reduction during the later weeks in each subgroup. The differences between categories in the amount of the drop in later weeks probably have no medical import. In neither

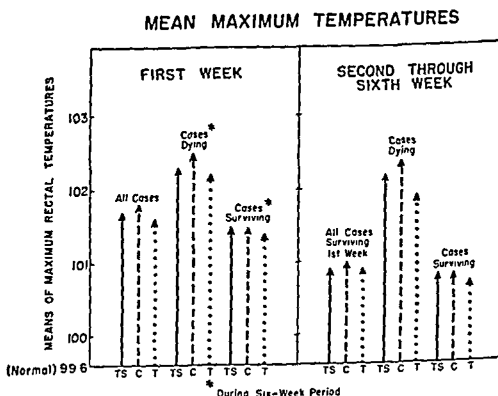


Figure 53. MEAN MAXIMUM TEMPERATURES: Means of maximum rectal temperatures reported for all cases, cases dying within six weeks, and cases surviving in the total sample and in the control and treated groups, by period of illness.

Differences between the control and treated group death rates in this period are particularly striking among those with high temperatures but because the groups were relatively small, no great reliance should be placed on the exact rates reported for this level.

The fact that the temperature is ordinarily elevated following an attack of acute coronary occlusion with myocardial infarction is certainly well recognized. Less clearly agreed on is the relative course of temperature in fatal and in nonfatal cases. Chambers[41] found that the average rectal temperature of fatal cases at the time of admission was 101.7 degrees Fahrenheit and that the temperature remained elevated until death. Fever was present without exception in fatal cases observed by him. The average rectal temperature among his patients who survived was slightly more than 100 degrees Fahrenheit. It fell to normal usually on the ninth or tenth day following the attack.

Tredway[m] found that both the average temperature and the range of temperatures at the time of admission were the same for fatal and for nonfatal cases. Fever following myocardial infarction in his patients did not differ between fatal and nonfatal cases in either duration or degree. About one-fifth of his patients who survived remained afebrile from the time of their acute attack, but only one patient who died failed to exhibit some febrile reaction.

Yater et al.[246] found elevated temperatures in 32 of 66 fatal cases and these temperatures remained elevated for longer periods of time than did the temperatures of survivors.

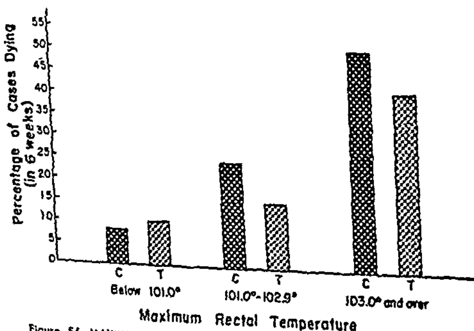


Figure 56. MAXIMUM TEMPERATURE LEVEL IN FIRST WEEK IN RELATION TO DEATH RATES. Percentage of cases dying within six weeks among cases in the control and treated groups with maximum rectal temperatures at various levels during the first week of the illness.

MAXIMUM TEMPERATURE, FIRST WEEK

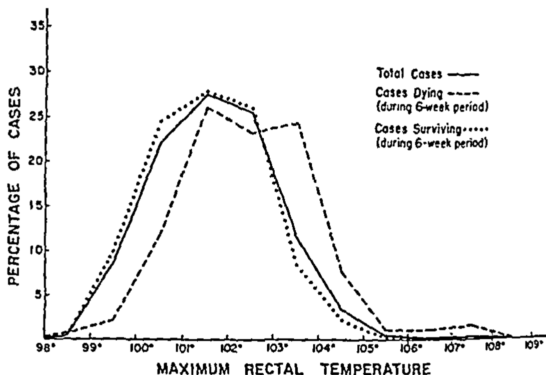


Figure 54. MAXIMUM TEMPERATURE, FIRST WEEK: Percentage of cases with maximum rectal temperatures at various levels during the first week among all cases in the total sample and among cases dying and cases surviving the six-week period.

MAXIMUM TEMPERATURE, SECOND THROUGH SIXTH WEEK

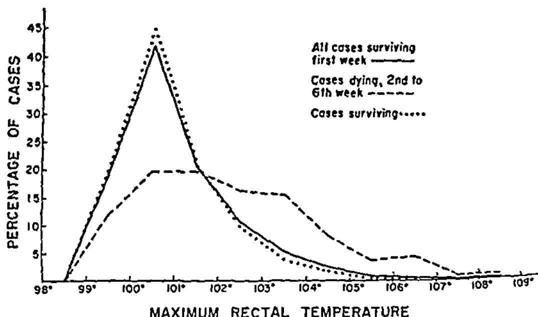


Figure 55. MAXIMUM TEMPERATURE, SECOND THROUGH SIXTH WEEK: Percentage of cases with maximum rectal temperatures at various levels during the second through the sixth week among all cases in the total sample surviving the first week, among cases dying during the second through the sixth week, and among cases surviving these weeks.

many cases, no report of the usual blood pressure was available.

The daily blood pressure readings during the present illness were copied from the daily hospital records, but on the early records were reported only in summary form after the third week. Only one systolic and one diastolic reading (presumably the average) was reported per day for each patient.

The "difference" between the lowest recorded systolic or diastolic blood pressure and the usual level existing prior to the present illness used for this analysis represents the difference between the lowest blood pressures (systolic or diastolic) reported for any hospital day during the specified period and the "usual" blood pressure reported in the patient's history. For purposes of brevity, these differences are referred to in the ensuing comment as "drops" in blood pressure since in most instances changes were in this direction.

Understatements of the difference occurred because patients were sometimes not hospitalized until the acute attack had passed and also because hospital readings may not have been taken at the lowest blood pressures for a given day. In a few patients, differences were based on only one or two hospital observations during the first week since hospitalization of these patients was delayed following the onset of the present illness.

Systolic Blood Pressure, First Week

Because reports of usual blood pressures were often lacking, the maximum drop in blood pressure during the first week could be computed for only 46 per cent of the cases. Among this 46 per cent, the lowest reported

MAXIMUM BLOOD PRESSURE DROPS

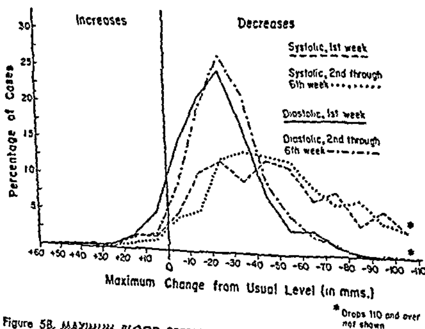


Figure 58. MAXIMUM BLOOD PRESSURE DROPS: Percentage of cases showing various differences between the average blood [illegible] day during the [illegible] pressure [illegible] whom a [illegible] level prior to the present illness was reported.

Among 274 survivors, 50 were completely afebrile.

Blood Pressure

It is generally recognized that a fall in blood pressure commonly follows myocardial infarction. These drops tend to occur promptly, a maximum fall in blood pressure being evident in most instances within 24 to 72 hours. Occasionally, however, the blood pressure will not reach a minimum reading for a matter of 7 to 10 days. Because of the importance of these drops, both in diagnosis and in prognosis, the reporting forms provided spaces specifically designated for the recording of (1) the usual blood pressure, systolic and diastolic, known to have existed prior to the present illness and (2) daily blood pressures, systolic and diastolic, reported in terms of average observations for each day for the six-week period of observation during the present illness.

The usual blood pressure prior to the present illness was sometimes known accurately by the personal observation of the attending physician, or was obtained from the hospital records of previous in- or out-patient visits. Sometimes it was provided by a physician referring the patient to the hospital because of the present illness. Occasionally, the information was obtained from the patient himself or from a member of his family. The accuracy of reported readings tended to vary widely according to the reliability of the respective sources of such information. In

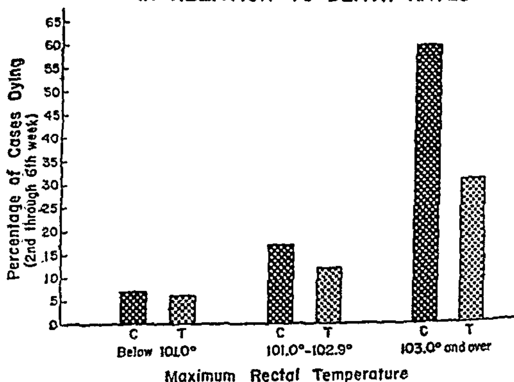


Figure 57. MAXIMUM TEMPERATURE LEVEL FROM SECOND THROUGH SIXTH WEEK IN RELATION TO DEATH RATES: Percentage of cases dying from the second through the sixth week of the illness among cases in the control and treated groups surviving to the second week and having maximum rectal temperatures at various levels during the second through the sixth week of the illness.

sample for both the first week and later weeks. The curves for systolic pressures are low and broad with distinct plateaus over the range of 10 to 59 mm. Hg.

The maximum drops for each case were also averaged after classification for treatment and survival status. The results are shown in Table 63 and Figure 59. The mean net drop in systolic blood pressure during the first week was 51 mm. Hg. It was greater among patients dying (66 mm. Hg) than among patients surviving (48 mm. Hg). There were no appreciable differences between the control and treated groups in the mean net drops for systolic blood pressure.

The basic data appear in Appendix F, Table 21 by treatment group and survival status. There is only an insignificant difference between the control and treated groups in respect to the percentage showing a fall in systolic blood pressure during the first week, the percentages being 93 and 94 per cent respectively. Other differences by treatment groups were similarly minor during the first week.

However, when persons dying and surviving are compared, contrasts are more marked. As Appendix F, Table 21 reveals, a higher percentage of patients dying suffered extreme drops in blood pressure than did those surviving, a contrast that is independent of treatment status. Thus an exceptionally large drop may indicate an unfavorable prognosis.

Figure 60, which shows death rates in relation to the amount of the drop in the systolic and diastolic blood pressures, shows this relationship in unmistakable terms. (The percentages of cases dying were computed from data in Appendix F, Table 21, the control group rates being corrected for exceptions in treatment.) Among those in the control group *showing maximum drops* of 60 mm. or more during the first week, 41

MEANS OF MAXIMUM BLOOD PRESSURE DROPS
IN FIRST WEEK

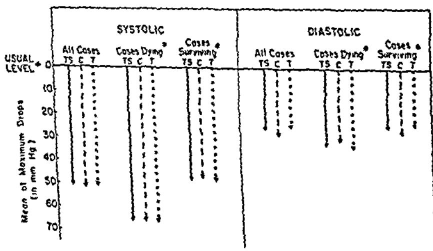


Figure 59. MEANS OF MAXIMUM BLOOD PRESSURE DROPS IN FIRST WEEK: Means of maximum drops in systolic and diastolic blood pressure during the first week of the illness among all cases, cases dying within six weeks, and cases surviving in the total sample and in the control and treated groups (drops measured in terms of the difference between the average blood pressure on the lowest hospital day and the usual level prior to the illness).

systolic blood pressure was higher during the first week of the present illness than it had been prior to the present illness in 4 per cent, the same in 3 per cent, and lower in 93 per cent. In the few instances in which the lowest day was above the previous usual level, the rise in systolic blood pressure was not of great magnitude. Mintz and Katz[112] reported that such rises are usually transitory. Seventy-four per cent of the cases exhibited falls in systolic blood pressure of between 10 and 79 mm. Hg, the largest drop being 180 mm. Hg. In the present study, hypertensives were not separately analyzed with respect to blood pressure drops. It is known, however, that falls in blood pressure tend to be greater in hypertensive persons than in normotensives, though the resulting pressures may still be at hypertensive levels.

The frequency of various differences between the lowest average systolic blood pressure observed during the first week and the usual level before the present illness is shown graphically in Figure 58 for the total

TABLE 63

MEANS OF MAXIMUM DROPS IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURES: Means of Maximum Drops in Systolic and Diastolic Blood Pressure for All Cases in the Total Sample and in the Control and Treated Groups for Whom a Blood Pressure Level Prior to the Present Illness Was Reported, by Period of Illness and Survival Status

Period of Illness and Treatment Group	*Mean of Maximum Blood Pressure Drops*[a]					
	Systolic			Diastolic		
	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six Week Period
First Week:						
Total sample	51	66	48	26	32	25
Control group	52	66	47	28	30	27
Treated group	51	66	48	25	33	24
Second through sixth week:						
Total sample	52[b]	61[b]	51	29[b]	43[b]	28
Control group	52[b]	*59*[b]	51	29[b]	*47*[b]	27
Treated group	53[b]	*64*[b]	52	29[b]	*40*[b]	28
	Number of Cases with Drops Known for Period					
First Week:						
Total sample	477	93	384	375	75	300
Control group	190	43	147	154	36	118
Treated group	287	50	237	221	39	182
Second through sixth week:						
Total sample	453	51	402	362	46	316
Control group	188	28	160	154	25	129
Treated group	265	23	242	208	21	187

Note: *Italics are used when means quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] Drops were measured in terms of the difference (in mms.) between average blood pressure on the lowest hospital day and usual level prior to the illness. Means were computed by subtracting total increases from total decreases and dividing by the number of cases in which the difference was known for the period in question.

[b] Means for the second through the sixth week necessarily exclude those in the first-week group who failed to survive to the beginning of the second week.

Falls in the average systolic blood pressure occurred over a wide range (see Appendix F, Table 22) only slightly less than that reported for the first week, the largest fall reported during the later weeks being 150 mm. Hg (as compared to 180 mm. Hg for the first week). Seventy-six per cent of the cases exhibited falls in systolic blood pressure of between 20 and 89 mm. Hg. The frequencies of various differences are shown in Figure 58 for the total sample. It is evident that the shape of the curve does not differ significantly from that of the first week. The slight shift of the curve for later weeks to the right of that for the first week suggests that average systolic pressures during later weeks were somewhat lower than those of the first week.

The mean net drop in systolic blood pressure for later weeks was 52 mm. Hg, an average almost identical with that for the first week. As Table 63 and Figure 61 show, the mean net drop in systolic blood pressure during the later weeks of the illness was greater among patients dying (61 mm. Hg) than among patients surviving this period of illness (51 mm. Hg). As in the first week, this greater mean net drop in systolic blood pressure among patients dying is compatible with the more frequent occurrence of shock and of heart failure in such patients.

Differences between the control and treated groups were negligible in all categories for the period and, considering the inaccuracies necessarily inherent in their method of computation, probably are without significance.

Ninety-six per cent of all cases in the total sample for whom comparison with levels prior to the illness could be made showed a fall in systolic blood pressure during later weeks. The difference between the control and treated groups in this respect was not statistically significant, the percentages being 97 and 96 per cent respectively. In contrast to the experience of the first week, when a definitely higher percentage of cases dying in the total sample showed a fall in

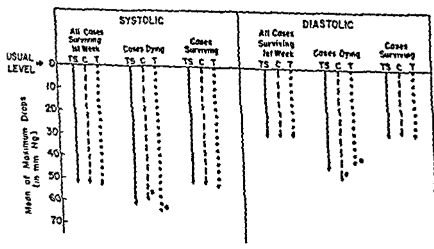


Figure 61. MEANS OF MAXIMUM BLOOD PRESSURE DROPS DURING SECOND THROUGH SIXTH WEEK: Means of maximum drops in systolic and diastolic blood pressure during the second through the sixth week among all cases in the total sample and in the control and treated groups surviving the first week, among cases dying during second through sixth week, and among cases surviving these weeks.

per cent died within the study period as compared with 18 per cent of those with drops of 20 to 59 mm. and 14 per cent with drops of less than 19 mm. or no drop. The corresponding percentages for the treated group were 30, 12 and 9 per cent. Whether the poor prognosis associated with large drops in blood pressure is due to the extent of the fall in blood pressure, or to the low levels of blood pressure which result, is not evident from the data as analyzed.

Systolic Blood Pressure, Second through Sixth Week

Blood pressure comparisons with the period before the attack were possible for 47 per cent of all cases surviving to the beginning of the second week. The lowest average systolic blood pressure was slightly higher during the second through the sixth week of the present illness than it had been prior to the present illness in 2 per cent, the same in 2 per cent and lower in 96 per cent of the cases.

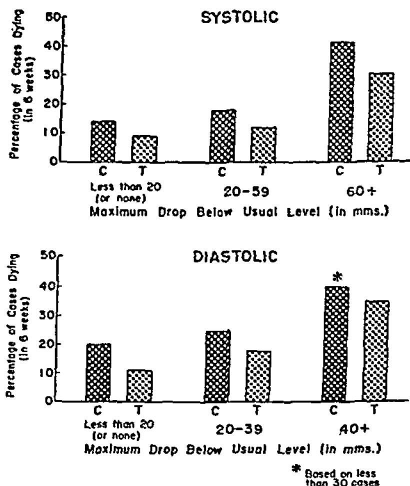


Figure 60. MAXIMUM BLOOD PRESSURE DROPS IN FIRST WEEK IN RELATION TO DEATH RATES: Percentage of cases dying within six weeks among cases in the control and treated groups showing maximum drops in systolic and diastolic blood pressure of various amounts during the first week of the illness (as measured in terms of the difference between average blood pressure on lowest hospital day in this period and usual level prior to the illness).

group the trend was more apparent, the corresponding death rates for the same drop intervals being zero, 8 and 13 per cent. In general, the relation seems less conspicuous than for the first week, but lack of adequate reports from which maximum drops could be computed for many cases makes all deductions risky.

Diastolic Blood Pressure, First Week

Comparisons for diastolic pressures with the period before the attack were possible for only 36 per cent of the cases. For these cases, the lowest average diastolic blood pressure was higher during the first week of the present illness than it had been prior to the present illness in 7 per cent (4 per cent for systolic pressure), the same in 5 per cent, and lower in 88 per cent. For all but 7 of these, the systolic pressure was also lower. On the other hand, 25 cases showed a drop in systolic pressure but no drop in diastolic pressure. Thus, a total of 355 cases, or 95 per cent of those for whom data were available, showed a drop in the diastolic or systolic pressure below the usual level. Elevations above previous levels exceeded 30 mm. Hg in only 2 cases.

Falls in diastolic blood pressures were in general less than those for systolic pressures and showed a smaller range. The largest fall in the average diastolic blood pressure reported during the first week was between 80 and 89 mm. Hg (as compared with 180 mm. Hg for systolic blood pressure). Eighty per cent of the cases exhibited falls between 1 and 49 mm. Hg (as compared with 49 per cent showing a systolic drop within this range).

The frequency of various differences for the total sample is plotted in Figure 58. The curve, in contrast to those for the systolic pressure, is high and peaked with a definite maximum at 20–29 mm Hg. The detailed figures are given in Appendix F, Table 21.

The mean net drops in diastolic blood pressure during the first week of the illness are given in Table 63 and shown graphically in Figure 59. The mean net diastolic drop for the period was 26 mm. Hg as compared with a similar figure for the systolic blood pressure of 51. This drop was greater among patients dying (32 mm. Hg) than among patients surviving (25 mm. Hg). There was no appreciable difference in the mean net drop for diastolic blood pressure between the control and treated groups.

Eighty-eight per cent of all cases in the total sample for whom comparison with prior periods could be made showed some fall in the diastolic blood pressure during the first week. There was an appreciable difference between the control and treated groups in this respect, the percentages being 85 and 90 per cent respectively, but the difference is not statistically significant. Cases dying showed a higher proportion of drops than those surviving in all categories. Ninety-four per cent of the control group and 95 per cent of the treated group for whom comparisons were possible showed a drop in both systolic and diastolic pressure. The difference was not statistically significant.

Figure 60 demonstrates in a more direct way this association between drops in diastolic blood pressure in the first week and prognosis. The death rates were computed from Appendix F, Table 21 in the same manner as the systolic rates. Among those in the treated group with maximum drops in diastolic blood pressure in this period of 40 mm. Hg or more, 35 per cent died within six weeks, as compared with only 18 per cent of those with maximum drops of 20 to 39 mm. Hg and 11 per cent of those with drops of less than 20 mm. Hg or no drop. The corresponding rates for the control group were 40, 25 and 20 per cent respectively (rates quoted are corrected for exceptions in treatment). *The poor prognosis associated with large drops in blood pressure is obvious as is also the consistently favorable record of the treated group.* It is not clear, however, whether the critical factor is the amount of

blood pressure than did those surviving, there was no difference whatsoever during the later weeks of the illness, the percentage in each instance being 96. This difference between the first and later weeks may reflect largely the longer period of observation with which to secure a low reading for survivors, the effects of bed rest, and the lack of sensitivity in the measure used.

The relation of maximum systolic blood pressure drops during the second through the sixth week to prognosis is more readily apparent in Figure 62 in which the data from Appendix F, Table 22 are converted into death rates in relation to maximum blood pressure drops. In contrast to the first week, there was no clear relation between deaths from the second through the sixth week and the amount of the drop for the control group. The corrected death rates portrayed for the control group were 17, 15 and 19 per cent of deaths among patients showing maximum drops of less than 20 (or none), 20-59, and 60 or more mm. respectively. For the treated

MAXIMUM BLOOD PRESSURE DROPS SECOND THROUGH SIXTH WEEK IN RELATION TO DEATH RATES

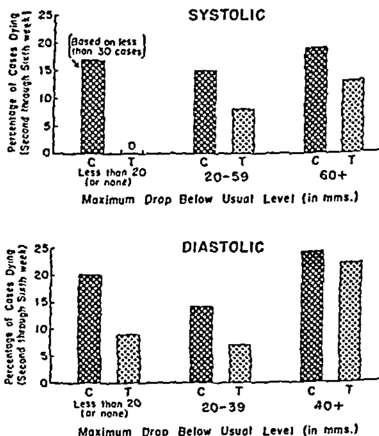


Figure 62. MAXIMUM BLOOD PRESSURE DROPS SECOND THROUGH SIXTH WEEK IN RELATION TO DEATH RATES: *Percentage of cases dying from the second through the sixth week among cases in the control and treated groups showing maximum drops in systolic and diastolic blood pressure of various amounts during the second through the sixth week (as measured in terms of the difference between average blood pressure on lowest hospital day in this period and usual level prior to the illness).*

cent for the treated group. The medical explanation of the relatively high death rates for patients showing little or no drop in diastolic blood pressure, or some rise, remains obscure. Caution in deductions is indicated since no drop figure could be computed for 72 persons dying during this period, while for others who died early in their illness, observations covered a relatively short period. The highest rates were again found among those with maximum drops of 40 mm. or more, the actual death rates being 24 per cent for the control group and 22 per cent for the treated group. *A large drop in blood pressure below usual levels appears once more to be an unfavorable sign regardless of the period of the illness in question.*

Prognosis in Relation to Absolute Blood Pressure Levels

Prognosis in myocardial infarction is related not simply to a fall in blood pressure, nor even to the extent of such a fall, but rather to whether or not the blood pressure falls below certain critical levels and to the length of time it remains below these levels. Although the shock syndrome was studied in the present series, the blood pressures associated with shock were not separately analyzed. Neither were the absolute levels of minimum blood pressure as such. The following assertions regarding pressure levels can, however, be made on the basis of the work of other authors:

1. Prognosis is grave if the systolic pressure falls below 100 mm. Hg and remains below this level for a period of 3 to 5 days.[152,191]

2. An extremely poor prognosis results when the systolic pressure falls to 80 mm. Hg or less and remains at such a level for a period of hours or days.[11, 89, 150, 204] Mintz and Katz[142] observed an extremely grave prognosis when pressures of 90 mm. Hg or less persisted for days.

3. Changes in pulse pressure appear to be unimportant until the pulse pressure falls to 20-25 mm. Hg. The prognosis then becomes exceedingly grave[143] and mortality increases to 50 per cent or more.[46, 152]

SUMMARY

The present chapter has presented the findings regarding the onset of the illness and its signs and symptoms. The following chapter continues the discussion and evaluation of the course of the illness with the analysis of data relative to syndromes during the illness, to laboratory findings and to miscellaneous conditions and complications during the illness (other than those of a thromboembolic or hemorrhagic character). In order that a more integrated summary of the findings and conclusions regarding the course of the illness may be presented, both this and the succeeding chapter are summarized as a unit at the end of Chapter VI.

the drop or the actual low level resulting from the drop since minimum levels were not separately tabulated. Since the amount of drop in diastolic pressure could not be computed for more than half the sample, the rates cited must be considered approximate only.

Diastolic Blood Pressure, Second through Sixth Week

Comparisons between the usual diastolic blood pressure before the present illness and the lowest day in later weeks were possible for 38 per cent of all cases surviving to the beginning of the second week. The lowest average diastolic blood pressure was higher during the second through the sixth week than it had been prior to the present illness in 4 per cent, the same in 3 per cent and lower in 93 per cent. Ninety-two per cent of all the cases showed drops in both systolic and diastolic pressure from the second through the sixth week and 97 per cent, a drop in either systolic or diastolic pressure. Elevations never exceeded 29 mm. Hg.

The maximum fall reported for the diastolic blood pressure during the later weeks was 120 mm Hg. Approximately 83 per cent of all cases exhibited a drop in diastolic blood pressure during later weeks of between 1 and 49 mm. Hg (the comparable figure for the first week of illness was 80 per cent). The details appear in Appendix F, Table 22. The falls in diastolic blood pressure during later weeks tended to be distinctly less than the falls in systolic blood pressure.

Distribution curves for these drops for the first and later weeks are shown in Figure 58 for the total sample. The two curves are markedly similar. The slight tendency for the curve for later weeks of the illness to shift to the right of that for the first week is evident as in the case of the systolic blood pressure. However, the shape of both curves for diastolic blood pressure differs strikingly from that for systolic. The former are highly peaked with a maximum at 20–29; the latter are low and extended with a relative plateau extending over the general range of 10-59.

The mean net drop in diastolic pressure in later weeks for these same cases was 29 mm. Hg. As Table 63 and Figure 61 show clearly, this net drop was greater among patients dying (43 mm. Hg) than among patients surviving (28 mm. Hg) in all categories, a fact that again suggests the close relation of blood pressure drops to prognosis.

Ninety-three per cent of all cases in the total sample for whom comparison could be made showed some fall in diastolic blood pressure during later weeks. There was no statistically significant difference between the control and treated groups in this regard, the percentages being 92 and 93 respectively. In both the control and the treated group, 97 per cent of the cases for whom data were available showed a drop in either systolic or diastolic pressure during this period.

In contrast to the first week, when the percentage showing a fall in blood pressure among cases dying exceeded the corresponding percentage for cases surviving, the relative position of those dying and those surviving was reversed in later weeks in both the control and treated groups. The meaning of this reversal is not obvious, but the longer period during which survivors could demonstrate a drop may well have been a factor.

A similar departure from the expected pattern occurs in Figure 62 which deals with death rates in relation to the amount of the maximum drop in systolic and diastolic pressures (see figure previously presented on p. 124, based on data from Appendix F, Table 22). *The lowest death rates for the second through the sixth week are seen to be associated with maximum drops of 20 to 39 mm. Hg in diastolic blood pressure.* The actual corrected death rates for this group were 14 per cent for the control group and 7 per cent for the treated group. A somewhat higher death rate was found for cases with drops of less than 20 mm., the actual death rates being 20 per cent for the control group and 9 per

whose reports revealed no evidence of any of these conditions (except dyspnea)* were assumed not to have shown congestive failure or shock. With full reporting in all instances, the number of patients with congestive heart failure and/or shock might have been higher.

Initial Heart Failure and Shock

It is well recognized that patients with coronary occlusion with myocardial infarction may develop signs and symptoms of congestive heart failure immediately or shortly after the attack, or they may suddenly develop acute congestive failure as the initial or only sign of the coronary occlusion. Acute pulmonary edema is particularly prone to occur. Mild or moderate degrees of preexisting heart failure may also be aggravated suddenly by the attack. In the majority of instances, an onset complicated by congestive failure occurs in patients who have experienced severe cardiac damage either with the present or a previous attack, or in whom a large or vital area of the heart has been infarcted. To be considered "initial" heart failure or shock for purposes of present tabulations, the reports must have indicated clearly that these syndromes were either aggravated, or appeared for the first time, during the first two days following the initial acute attack. Since the onset of initial heart failure and initial shock was in most cases prior to the beginning of anticoagulant therapy, the incidence of these syndromes initially may be used as an approximate indication of the comparability of the control and treated groups in respect to degree of initial and/or prior cardiac damage.

The proportion of patients responding to the initial attack with heart failure or shock or both is given in Table 64 and Figure 63 by severity at onset. In Figure 63 the vertical shading represents initial heart failure; the horizontal shading, initial shock; and the overlapping of the two grids, both congestive heart failure and shock. The detailed counts appear in Appendix F, Table 23.

Twenty-one per cent of the cases in the total sample suffered from initial heart failure, 20 per cent, from initial shock, and 7 per cent, from both. These percentages may be utilized by the reader to visualize the approximate severity of cases in this series; however, if they are so used, *it must be remembered that the sample included only hospitalized cases who survived the first twenty-*

TABLE 64

[illegible] HEART FAILURE [illegible] TO [illegible] Per- [illegible] ive [illegible] nts [illegible] and [illegible] or [illegible] Moderate at Onset and among Patients Whose Illness Was Severe

Severity of Illness at Onset and Treatment Group	Number of Cases	Percentage of Cases* Developing during the First Two Days of Their Illness— Congestive Heart Failure (with or without Shock)	Shock (with or without Congestive Heart Failure)	Both Congestive Heart Failure and Shock
Mild or moderate:				
Total sample	734	16.2	15.1	3.3
Control group	326	19 6	15.0	3.7
Treated group	408	13.5	15.2	2.9
Severe:				
Total sample	297	33.7	31.6	14.8
Control group	116	37.1	31.0	16.4
Treated group	181	31.5	32 0	13.8
All cases:				
Total sample	1031	21.2	19.9	6.6
Control group	442	24.2	19.2	7.0
Treated group	589	19.0	20.4	6.3

* Based on total cases in each subgroup. Counts include only cases for whom reports of heart failure symptoms or shock clearly indicate that they occurred during the first two days. They include cases with only mild symptoms, cases whose heart failure symptoms began prior to initial attack, and cases in whom hepatomegalia was the only symptom of heart failure.

* Dyspnea in the absence of these other symptoms could be explained on the basis of anxiety or [illegible]ient conditions.

CHAPTER VI

The Course of the Present Illness (*Continued*): Part 2. Syndromes, Laboratory Findings and Miscellaneous Complications

THE present chapter continues the presentation of the data relative to the course of the illness begun in the preceding chapter. It discusses in sequence the syndromes of congestive heart failure and shock, various laboratory observations during the illness, and miscellaneous diseases and conditions complicating the illness, with the exception of those directly related to anticoagulants (thromboembolic complications and hemorrhages) which are discussed in detail in later chapters. The data serve as previously the multiple purposes of (1) characterization of myocardial infarction, (2) evaluation of the sample and (3) exploration of incidental and indirect consequences of anticoagulant therapy.

SYNDROMES OF THE PRESENT ILLNESS

Congestive Heart Failure and Shock

Most observers agree that in myocardial infarction persistent congestive heart failure and shock are grave prognostic signs. As such, these syndromes deserve careful study. In the preceding sections, pulmonary and peripheral edema, dyspnea, and hepatomegaly have each been analyzed separately without regard for the total picture. In the present section, data on these same basic signs and symptoms are again utilized, but the focus is on the total syndrome. Consideration is given to (1) the extent and degree to which cases in this series suffered from congestive heart failure, (2) the relation of this syndrome to the age and previous heart failure record of the patient, and (3) any differences between the control and treated groups that might point either to a bias in the sampling or to interrelations between the incidence of congestive heart failure and anticoagulant therapy. Data on shock, a subject not previously discussed, are also presented, together with some indication of the extent to which both heart failure and shock were present in the same patient.

In the preparation of the present section, the case reports were reviewed and each case classified as to the presence or absence of congestive failure, its type (right, left, or both) and severity (one to four degrees), and the time and circumstances of its development. The findings are presented in subsections which deal consecutively with this phenomenon at various stages of the illness. Corresponding findings for shock at the same stages of the illness are also presented. Counts throughout include cases that developed only mild symptoms, cases of heart failure whose symptoms had been manifest prior to the onset of the attack, and cases in whom the only sign of a failing heart was hepatomegaly. Since the master forms specifically asked for data on shock, pulmonary edema, peripheral edema, dyspnea, hepatomegaly, and digitalis administration, cases

each of these conditions in the severe cases was about double that for the mild or moderate. For the combination of both heart failure and shock, the percentage for the severely ill was nearly five times that for those mildly or moderately ill at onset. Probably physicians, in evaluating severity, made appropriate use of these symptoms, among others, in appraising the amount of myocardial damage. The division of cases by severity at onset also serves to indicate that the discrepancies between the percentages or the control and treated groups were primarily in the mild and moderate, rather than in the severe, category, whereas the severe category is the more crucial from the point of view of the outcomes under study.

Figure 64, which deals with the total sample only and is based on data in Appendix F, Table 23, also indicates the relation of initial congestive heart failure and initial shock to age within *severity* groups. As before, the horizontal shading represents shock; the vertical shading, heart failure; and the overlapping area, both syndromes in the same patient. The prominence of heart failure and shock in the cases *reported* as severe at onset remains as in Figure 63. With a single, probably insignificant, exception, *both severity groups showed a consistent increase with age in the percentage of cases suffering from initial heart failure.* This adverse relation to age may be assumed to reflect the general accumulation of cardiac defects with advancing age, a trend which is similarly reflected in an increase in the proportion of cases with a prior history of heart failure from 8 per cent in the fifth decade to 21 per cent in the eighth decade.

In contrast to the age trends for heart failure, totals for initial shock showed, in general, little change with age, but the proportion of patients for whom shock was complicated with heart failure on the whole did increase with age. *It is noteworthy also that the proportion of severely ill patients below age 50 who showed shock was excessive*—in fact, included about half of all such patients. Although caution is indicated because of the smallness of the sample (51 cases only), this high proportion nevertheless suggests that very young patients are perhaps less able in this respect than their seniors to withstand the impact of myocardial infarction. Perhaps their lack of collateral coronary circulation is a factor since such collateral circulation helps to limit the area of infarction and perhaps the completeness of the death of tissue in an area rendered ischemic. Whatever the explanation, *the chances that a patient will succumb to shock immediately after the initial attack at least do not show a consistent increase with age.*

A further analysis of initial heart failure appears in Table 65 and graphically in Figure 65, where the reaction during the first two days is tabulated in relation to the previous history of heart failure. It is obvious that cases with a prior record of heart failure have a very much greater chance of developing initial heart failure under the stress of a myocardial infarction than do patients with no record of past heart failure. Among cases in the total sample with a known history of heart failure, more than half (56 per cent) gave evidence of heart failure within two days of the onset of the attack, whereas only 15 per cent of those with no such history showed initial heart failure. *In other words, previous cardiac damage serious enough to produce failure greatly lessens the chances that a patient can maintain compensation under the impact of a myocardial infarction.*

It is further apparent from Figure 65 that the total difference between the control and treated [illegible] di[illegible] w[illegible]ious heart failure. The record for more handicapped patients, namely those with a prior history of heart failure, is exactly equal (56 per cent) for both the control and treated groups.

The extent to which initial heart failure and shock can be used as a basis for prognosis with respect to chances for survival and thromboembolic complications is dis-

four hours of hospitalization. Some coronary attacks are so mild that the patient is never hospitalized, while others are so severe that the patient dies almost immediately. Inclusion of cases at either of these extremes would have altered very substantially the rates reported.

Initial heart failure was somewhat more frequent in the control than in the treated group (24 per cent, control, *vs.* 19 per cent, treated). While this difference is not large enough to reach statistical significance as defined for this study, it is sufficient to raise the suspicion that perhaps occasional physicians, fearing to risk anticoagulant therapy with cases in congestive failure, may have arranged that a few such cases be included in the control group. The balance was reversed in the case of shock. Initial shock was shown a little more frequently by the treated group than by the control group (19 per cent, control, *vs.* 20 per cent, treated). Either one or the other or both of these syndromes were present during the first two days in 36 per cent of the control group and 33 per cent of the treated group. The differences again are not statistically significant. In view of the complexity of these phenomena, inaccuracies in reporting, etc., these differences probably also have little or no significance for the outcome of the study.

Figure 63 also reveals a close association between the presence of congestive heart failure and/or shock during the first two days and the physician's evaluation of the severity of the attack at onset. The rate for

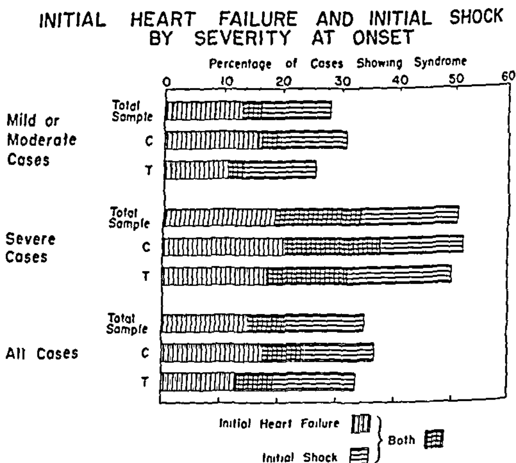


Figure 63. INITIAL HEART FAILURE AND INITIAL SHOCK BY SEVERITY AT ONSET: Percentage of cases in the total sample and in the control and treated groups who experienced congestive heart failure or shock or both during the first two days of the illness among all cases and among cases whose illness was mild or moderate at onset or severe at onset.

cussed in Chapters XI and VIII. As is pointed out in these chapters, the value of these syndromes for prognosis is limited by their often relatively temporary character. *Initial heart failure disappeared within three* days and was not reported as recurring during the period of observation *in 45 per cent* of the control group and 42 per cent of the *treated group with this syndrome. Another* 23 per cent of the control group and 22 per cent *of the treated group regained compensation* within the first week and showed no more congestive failure thereafter during the six-week period of observation. *It is, therefore, not to be assumed that patients beginning in heart failure will necessarily remain uncompensated.*

Heart Failure and Shock during the Entire First-Week Period

The record for the total first week, the time unit used in reports of other symptoms, *is the net result of the record during the* first two days, plus developments during the next five days. About 12 per cent of the cases not showing initial heart failure developed heart failure before the end of the first week, and an additional 7 per cent developed shock for the first time in this later period. When added to the totals for initial heart failure and shock, these cases brought the total number of cases showing heart failure at any time during the first week to 31 per cent of the total sample, and the total number of cases showing shock at any time during the first week to 26 per cent (see Tables 66 and 67, Appendix F *Table 24*, and Figures 66 and 67). The control group was slightly *higher than the treated group on congestive* heart failure (33 per cent, control *vs.* 29 per cent, treated) and also on shock (27 per cent, control, *vs.* 26 per cent, treated). The differences between the two groups were again not statistically *significant* for either heart failure or shock.

These percentages for the control and *treated* groups approach each other even more closely when consideration is limited

INITIAL HEART FAILURE
IN RELATION TO PRIOR HEART FAILURE

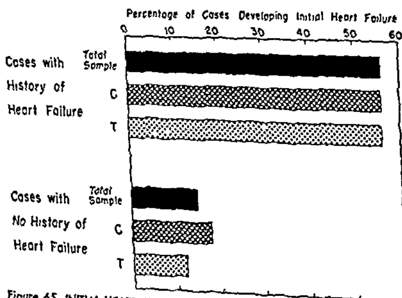


Figure 65. INITIAL HEART FAILURE IN RELATION TO PRIOR HEART FAILURE. Percentage of cases in the total sample and in the control and treated groups who experienced congestive heart failure during the first two days of the illness among patients with and without a previous history of heart failure.

INITIAL HEART FAILURE AND INITIAL SHOCK IN RELATION TO SEVERITY AT ONSET, BY AGE

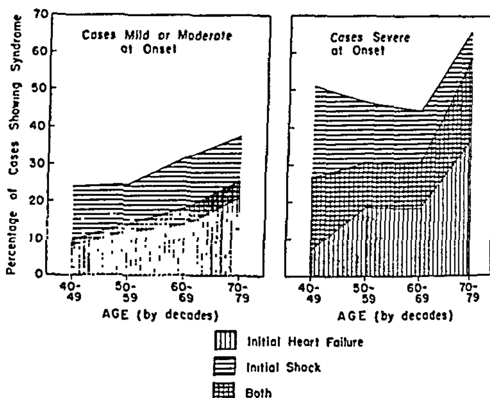


Figure 64. INITIAL HEART FAILURE AND INITIAL SHOCK IN RELATION TO SEVERITY AT ONSET, BY AGE: Percentage of cases in the total sample who experienced congestive heart failure or shock or both during the first two days of their illness among cases whose illness was mild or moderate at onset or severe at onset, by age.

TABLE 65

INITIAL CONGESTIVE HEART FAILURE IN RELATION TO STATUS OF CONGESTIVE HEART FAILURE PRIOR TO THE ATTACK: Number and Percentage of Patients Developing Congestive Heart Failure during the First Two Days after the Attack among Patients in the Total Sample and in the Control and Treated Groups with and without a Previous History of Congestive Heart Failure

Status of Congestive Heart Failure Prior to the Attack	Number of Cases			Cases Developing Congestive Heart Failure[a] during the First Two Days after the Attack: Number of Cases			Percentage of Cases[b]		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
Heart failure reported in history	148	66	82	83	37	46	56	56	56
No heart failure reported in history	853	364	489	126	65	61	15	18	12
Status of prior heart failure unknown	*30*	12	*18*	*10*	*5*	*5*	33	*42*	*28*
Total cases	1031	442	589	219	107	112	21	24	19

Note: *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such rates particularly unstable.*

[a] For definition, see footnote a, Table 64.

[b] Based on total cases in each subgroup.

same percentage of such cases, namely, 13 per cent. *This remarkable similarity would seem to indicate that the control and treated groups entered the period of active testing of anticoagulants (second through the sixth week) with closely similar proportions of persons with seriously damaged hearts.*

Table 66, Appendix F Table 24, and Figure 66 report the type of heart failure characteristic of the first week of illness. From Table 66 it can be computed that nearly half (45 per cent) of the cases with heart failure in the total sample showed left heart failure only; about a fourth (24 per cent), right heart failure only; and the remaining, both left and right heart failure (31 per cent). As indicated in Figure 66, the control and treated groups were closely similar in respect to type of heart failure.

Shock during the first week was usually mild to moderate in severity. Of those showing shock, 31 per cent showed a maximum severity of one degree; 37 per cent, two degrees; 17 per cent, three degrees; 12 per cent, four degrees. A residual 3 per cent could not be classified as to degree. Except for the fourth degree, the control group was again closely comparable to the treated, as Table 67 and Figure 67 indicate.

Heart Failure and Shock during the Second through the Sixth Week

After the first week, heart failure and shock were much less common syndromes than in the first week, and also were less adequately reported. Some who had presented the most acute conditions initially did not survive to begin their second week, while most others had begun to recover. The percentage of patients with heart failure of any type or degree after the first week dropped from 31 to 19 per cent, while the

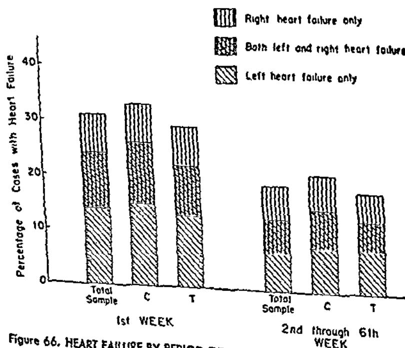


Figure 66. HEART FAILURE BY PERIOD OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups showing left or right heart failure, or both during the first week and from the second through the sixth week of the illness.

to the group showing prolonged heart failure not obviously related to complications. This group was defined to include all persons who survived to the beginning of the second week and showed heart failure both in the first and in later weeks, except those whose heart failure in later weeks developed shortly after a thromboembolic episode and seemed related to it. It was assumed that this group consisted largely of patients with severe cardiac damage and that its number was little influenced by anticoagulant therapy. It is interesting, therefore, that the control and treated groups each contained exactly the

TABLE 66

CONGESTIVE HEART FAILURE, BY PERIOD OF ILLNESS AND TYPE: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Various Types of Congestive Heart Failure during the First Week and from the Second through the Sixth Week of Observation

Type of Congestive Heart Failure[a]	Percentage of Cases					
	1st Week			2nd through 6th Week		
	Total Sample (1031 Cases)	Control Group (442 Cases)	Treated Group (589 Cases)	Total Sample (959 Cases)	Control Group (410 Cases)	Treated Group (549 Cases)
None[b]	69	67	71	81	79	82
Left heart failure only	14	15	13	7	8	8
Right heart failure only	7	7	7	6	6	5
Both left and right heart failure	10	11	9	6	7	5
All cases	100	100	100	100	100	100

[a] Since the original form did not contain a direct question regarding heart failure, the classification of cases is based on symptoms reported and drugs prescribed Cases with hepatomegalia only were considered to have right heart failure.

[b] Including occasional cases for whom the reporting of symptoms was too inadequate to make possible a fully certain classification

TABLE 67

DEGREE OF SHOCK, BY PERIOD OF ILLNESS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Shock of Various Degrees during the First Week and from the Second through the Sixth Week of Observation

Maximum Degree of Shock Reported at Any Time	Percentage of Cases[a]					
	1st Week			2nd through 6th Week		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
None	74	73	74	96	95	96
Mild to moderate (1st or 2nd degree)	18	18	18	1	2	1
Moderate to severe (3rd or 4th degree)	7	8	7	2	2	2
Degree unknown	1	1	1	1	1	1
Total with report on shock	100	100	100	100	100	100
	Number of Cases with Report on Shock					
Total cases at beginning of the period	1013	433	580	937	400	537

[a] Based on number of cases with a report on shock

reflected indirectly in a lower percentage of cases showing heart failure in the treated group during the second through the sixth week among those survivors who began this period with no record of heart failure in the [illegible] 6.0 per [illegible] robably [illegible] of this amount and in this direction can be expected on a chance basis only slightly less than three times in a hundred in samples of these sizes. Correspondingly defined rates for new shock from the second through the sixth week were 4.4 per cent for the control group and 2.1 per cent for the treated group. The reductions in both syndromes were apparently due in considerable measure to the reduction in thromboembolic complications.

A test for a possible benefit of this type in the present series was difficult and could only be approximated since the available records were not such as would permit a detailed study of fluctuations in the severity and duration of heart failure and shock with variations in anticoagulant therapy. The only approach that seemed possible was again that of determining whether more patients in the control than in the treated group who escaped heart failure and shock during the first week developed heart failure or shock from the second through the sixth week. Cases who had showed shock or heart failure during the first week were again eliminated since many such patients might be expected to continue to show these syndromes in later weeks. Under these circumstances, an evaluation of the effect of anticoagulants would require more detailed information on the course, severity, and duration of these syndromes than was available. It was assumed, moreover, that patients selected because they had not shown these symptoms under the stress of the original attack could be considered well equated as to basic cardiac strength. Since interest in this second test centered on possible benefits from anticoagulant therapy that were *not* related to their power to minimize thromboembolism, all cases were also eliminated in this instance from both the control and treated groups who had developed any clinically diagnosed thromboembolic complications at any time during the illness. This test differs from the test just described in this respect only. The results are given in Table 68 and Figure 68.

Patients in this component of the treated group, even though they appeared clinically not to have suffered from any thromboembolic complications, nevertheless made a somewhat better showing than the corresponding control group on both new heart failure and new shock. This favorable as-

TABLE 68

CONGESTIVE HEART FAILURE AND SHOCK AFTER THE FIRST WEEK IN THE ABSENCE OF THROMBOEMBOLIC COMPLICATIONS: Percentage of Cases Developing Congestive Heart Failure and Percentage of Cases Developing Shock at Any Time during the Second through the Sixth Week of Their Illness among Patients in the Control and Treated Groups Surviving the First Week Who Showed No Congestive Heart Failure or No Shock during the First Week after the Attack and No Thromboembolic Complications at Any Time during the Illness

Treatment Group	Cases Surviving to Beginning of Second Week and Showing No Thromboembolic Complications at Any Time					
	Cases Showing No Congestive Heart Failure[a] in 1st Week			Cases Showing No Shock in 1st Week		
	Total Cases	Cases Developing Congestive Heart Failure during 2nd through 6th Week		Total Cases	Cases Developing Shock during 2nd through 6th Week	
		Number	Per Cent[b]		Number	Per Cent[c]
Control group	208	17	8.2	235	7	3 0
Treated group.	363	19	5.2	377	4	1.1

[a] For definition of cases considered to show heart failure, see pages 128-129.

[b] Based on counts in Column 1.

[c] Based on counts in Column 4.

percentage of patients with shock of any degree dropped from 26 to 4 per cent (see Tables 66 and 67, Appendix F Table 24, and Figures 66 and 67). The drop in heart failure was primarily among those showing left heart failure only or left heart failure in combination with right heart failure. Little improvement was demonstrated in the category for right heart failure only. In the case of shock, all degrees of severity showed very substantial reductions, but those who did show shock after the first week more frequently reached third and fourth degree levels of severity. Differences between the control and treated groups in the over-all proportions showing heart failure or shock from the second through the sixth week favored the treated group but were again not statistically significant.

Effect of Anticoagulant Therapy on New Heart Failure and Shock

A particularly interesting and important question with regard to heart failure and shock in this study is: Do anticoagulants improve in any way the patients' prospects of avoiding heart failure or shock or of lessening their intensity? The possibility of avoiding heart failure and shock by preventing thromboembolic complications, such as extensions or new infarctions in the myocardium which may precipitate these conditions, is obvious. The success of anticoagulants in preventing thromboembolic complications is dealt with in Chapter VIII, and their effect on deaths is dealt with in Chapter XI.

In the present section, the effect of anticoagulants on thromboembolic phenomena

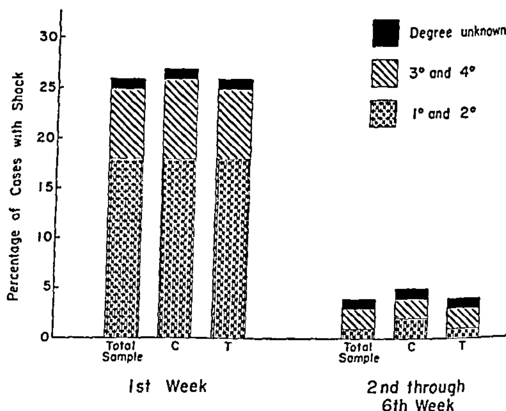


Figure 67. SHOCK BY PERIOD OF ILLNESS: Percentage of cases in the total sample and in the control and treated groups experiencing shock of various degrees during the first week and from the second through the sixth week of the illness.

in the incidence of undiagnosed thromboembolic complications as, for example, pulmonary infarctions diagnosed as pulmonary edema, or undiagnosed extensions of the original infarctions. Since most of the patients included in this analysis survived the illness, the extent of such hidden influences could not be ascertained. *From the present data it can only be concluded that anticoagulants have no unfavorable effect on the prospect of new heart failure or shock after the first week in myocardial infarction cases and may actually play a limited beneficial role.*

Effect of Anticoagulants on Terminal Heart Failure

The possibility of a relation between anticoagulant therapy and terminal heart failure was also studied. "Terminal heart failure" was defined to include any heart failure that became progressively more severe during the last three days before death, regardless of whether such heart failure was a new symptom or was merely an aggravation at that time of a prior process. Heart failure augmented at this time was a fairly common characteristic of patients in this series who did not survive their illness. Of deaths in the treated group, 32 per cent were preceded by terminal heart failure, but only 24 per cent of those dying in the control group showed terminal heart failure as thus defined. The percentages for the treated group were higher in both left and right heart failure, as well as in the two types of failure combined[b]

On the surface this difference would appear to reflect adversely on the use of anticoagulant therapy in moribund cases, but the explanation is relatively clear and simple. Since deaths due to thromboembolism were greatly reduced in the treated group but deaths due to the severity of the original infarction could not be prevented by such therapy, it is to be expected that a larger *proportion* of the treated than of the control group *deaths* would be characterized by terminal heart failure. When deaths preceded by terminal heart failure are computed as a *percentage of total cases observed*, instead of as a percentage of deaths only, the percentage of cases demonstrating terminal heart failure becomes almost identical in the two groups, namely, 5.2 in the control group and 5.1 in the treated group. *The proportion of myocardial infarction cases who will die with evidence of terminal heart failure prior to death thus appears to be unaltered by anticoagulant therapy.* Except for (1) a favorable influence on thromboembolic complications (see Chapter VIII) and (2) the increased risk of excessively prolonged prothrombin times which may result from impairment of kidney or liver function, *there is no evidence that anticoagulant therapy affects either favorably or unfavorably the terminal type of heart failure that frequently precedes death.*

Heart Failure Any Time during the Total Six-Week Period

Data presented thus far have concerned heart failure and/or shock at particular stages of the illness. When the experience of this series with these syndromes is retabulated and cases showing heart failure *at any time* during the six-week period are counted as heart failure cases, a failing heart is found to be a common sequel to myocardial infarction of the type studied. Thirty-seven per cent of the total sample showed heart failure of some degree at some time either in the first week or in later weeks or both. For the control group this percentage was 40 per cent and for the treated group, 34 per cent. This difference is of borderline significance statistically.

This more than usual contrast by treatment groups appears to have been produced

[b] In the control group 23 deaths were characterized by terminal heart failure (16, left heart failure only, 2, right heart failure only, and 5, both types) In the treated group, 30 deaths were preceded by terminal heart failure (20, left heart failure only; 3, right heart failure only; and 7, both types).

sociation with anticoagulant therapy is consistent with that reported for complications, but the contrasts are less marked. In the control group, about 8 per cent of the cases who showed no heart failure during the first week developed heart failure in subsequent weeks, but in the comparable treated group component, only about 5 per cent developed new heart failure after the first week. Differences in the case of new shock followed a similar pattern. Three per cent of the cases in the control group who showed no shock during the first week developed shock during the second through the sixth week, as compared with about 1 per cent of the treated group. Neither difference is statistically significant for samples of this size.

This lack of proof of a true difference between the control and treated groups does not, however, preclude the possibility that a true difference does exist. The fact, for example, that the findings for shock are consistent with the observation of Gilchrist[1] that the early and efficient use of anticoagulants appears to influence favorably the outcome of the shock syndrome, suggests that the observation in this case may not be a chance one. In any case, the differences are sufficiently marked and consistent to warrant thought as to their possible meaning. Clearly they cannot be explained by the presence of selective factors favoring the treated group since such selection as the procedure provided for would have operated to place the treated group at a disadvantage (i.e., fewer of the seriously ill patients were eliminated from the counts either by death or the development of thromboembolic complications). Neither can the result be definitely attributed to an anticoagulant effect since all cases with clinically diagnosed complications were eliminated from both groups. Possibly the differences are due to a difference between the control and treated groups

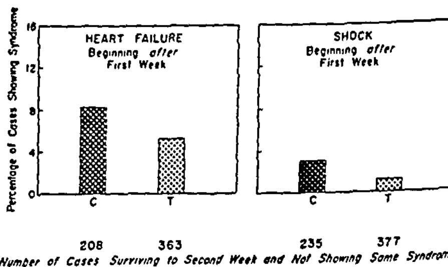


Figure 68. NEW HEART FAILURE AND NEW SHOCK AFTER THE FIRST WEEK: Percentage of cases developing congestive heart failure for the first time during the second through the sixth week among patients in the control and treated groups with no heart failure in the first week and no thromboembolic complications at any time, and corresponding percentages for shock among patients with no shock in the first week and no thromboembolic complications at any time.

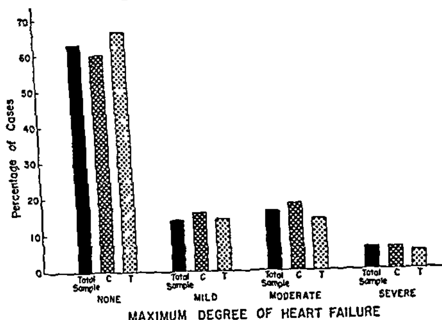


Figure 69. DEGREE OF HEART FAILURE: Percentage of cases in the total sample and in the control and treated groups showing maximum heart failure of various degrees during the six-week period of observation.

TABLE 70

TYPE OF CONGESTIVE HEART FAILURE, BY AGE: Percentage of Cases in the Total Sample Showing Various Types of Congestive Heart Failure during the Six-Week Period of Observation, by Age

Type of Congestive Heart Failure[a]	Percentage of Cases[b]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
None[c]	63	*80*	77	65	61	48	*47*	—[d]
Left heart failure only	16	*4*	12	16	16	23	*16*	—[d]
Right heart failure only	9	*8*	5	8	9	9	*16*	—[d]
Both left and right heart failure	12	*8*	6	11	14	20	*21*	—[d]
Total cases	100	*100*	100	100	100	100	*100*	—[d]
	Number of Cases							
Total cases	1031	26	166	370	305	142	19	3

Note *Italics are used when percentages quoted are based on less than 30 cases since chances factors render such rates particularly unstable*

[a] See footnote a, Table 66.

[b] Based on number of cases in age subgroup.

[c] See footnote b, Table 66.

[d] Not computed since there were fewer than 10 cases in the sample

by a combination of (1) the effects of anticoagulant therapy as reflected in a lower rate of new heart failure in the treated group during later weeks (see Table 68), and (2) a slight difference in the original samples, as reflected in the relatively high percentage of the control group showing initial heart failure, particularly control patients who were only mildly or moderately ill at onset (see Table 64) and control patients with no previous record of heart failure (see Table 65).

To demonstrate the role of original sampling (factor 2) in the production of this difference, the consequences of eliminating artificially most of the effects of anticoagulant therapy were explored. The method involved equalizing statistically the rate of development of *new* heart failure from the second through the sixth week among cases in both groups who showed *no* heart failure in the first week.[a] With this adjustment, the percentage of cases in the treated group with heart failure at any time became 38 instead of 34 per cent, or only 2 per cent less than the corresponding percentage for the control group. This small remaining difference may be assumed to be the result of any or all of the following factors: (1) the original assignment of cases, (2) minor difference in the reporting of heart failure, and (3) chance. Which of the three was involved is of small import since the residual difference after this correction falls in any case so far short of statistical significance that it could easily be due to chance factors alone. *In other words, a statistically significant bias with respect to heart failure in the original selection of cases for the two treatment groups was not demonstrated.*

The proportion of heart failure cases in which the maximum degree of heart failure of any type at any time during the illness was at the mild, moderate, or severe level is shown in Table 69 and Figure 69, by treatment groups. These are based in turn on the counts in Appendix F, Table 25. Moderate heart failure was the most frequent maximum reached and mild heart failure, the next most frequent. Differences between the control and treated groups were slight and were confined to the mild and moderate categories.

Table 70 and Figure 70 analyze heart failure during the total period observed by type of heart failure and age. The detailed counts appear in Appendix F, Table 25. Left heart failure only was again the most common type, being characteristic of more than two-fifths of those with heart failure. Another third showed both right and left heart failure. Right heart failure only was the least common. All types showed a marked increase with age, nearly or more than doubling in four decades. A particularly large jump occurred between the seventh and the eighth decades. *Heart failure thus constitutes*

TABLE 69

DEGREE OF CONGESTIVE HEART FAILURE, BY TREATMENT GROUPS: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Congestive Heart Failure of Various Degrees during the Six-Week Period of Observation

Maximum Degree of Congestive Heart Failure Reported at Any Time	Percentage of Cases[a]		
	Total Sample	Control Group	Treated Group
None	63	60	66
Mild	14	16	14
Moderate	16	15	14
Severe	6	6	5
Degree unknown	1	—	1
Total with heart failure	*37*	*40*	*34*
	Number of Cases		
Total cases	1031	442	589

[a] Based on number of cases in each subgroup.

[a] Estimated by assuming that cases in the treated group who showed no heart failure in the first week (400 cases) developed heart failure during the second through the sixth week at the same rate as did the corresponding component of the control group (11.0 per cent, based on 283 cases) instead of at their own rate (6 0 per cent).

TABLE 71

DEGREE OF SHOCK, BY TREATMENT GROUPS· Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Shock of Various Degrees during the Six-Week Period of Observation

Maximum Degree of Shock Reported at Any Time	Percentage of Cases[a]		
	Total Sample	Control Group	Treated Group
None	71	70	73
Mild to moderate:			
One degree	9	9	8
Two degrees	10	11	9
Total mild to moderate	19	20	17
Moderate to severe:			
Three degrees	5	4	5
Four degrees	4	5	4
Total moderate to *severe*	9	9	9
Degree unknown	1	1	1
Total with shock	29	30	27
	Number of Cases with Report on Shock		
Total cases	1015	435	580

[a] Based on number of cases with a report on shock

heart failure, the percentage of patients in the treated group showing shock at any time becomes 29 per cent,[d] a figure practically the equivalent of the 30 per cent rate for the control group. Initial shock was actually higher in the treated than in the control group (see Table 64). Therefore, even though the difference in actual percentages for the total period is not sufficient to be statistically significant, *one can perhaps surmise that it reflects the favorable influence of anticoagulants on thromboembolic complications*, for such complications sometimes precipitate a recurrence of shock symptoms during the later stages of the illness. Other beneficial effects may also be present (see Table 68).

With respect to the severity of shock, no difference exists by treatment groups. Sixty-five per cent of both the control and treated group cases of shock never exceeded mild or moderate severity—a remarkable similarity. Detailed counts by treatment groups and

[d] Estimated by assuming that cases in the treated group who showed no shock in the first week (423 cases) developed shock during the second through the sixth week at the same rate as the corresponding component of the control group (4.4 per cent, based on 318 cases) instead of at their own rate (2.1 per cent).

TABLE 72

DEGREE OF SHOCK, BY AGE Percentage of Cases in the Total Sample Showing Maximum Shock of Various Degrees during the Six-Week Period of Observation, by Age

Maximum Degree of Shock Reported at Any Time	Percentage of Cases[a]							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
None	71	*65*	71	75	69	69	*68*	—[b]
Mild to moderate (1st or 2nd degree)	19	*31*	20	18	19	15	*21*	—[b]
Moderate to severe (3rd or 4th degree)	9	*4*	8	6	10	15	*11*	—[b]
Degree unknown	1	—	1	1	2	1	—	—[b]
Total with report on shock	100	*100*	100	100	100	100	*100*	—[b]
	Number of Cases with Report on Shock							
Total cases	1015	26	166	302	302	137	19	3

Note: *Italics are used when percentages quoted are based on less than 50 cases since chance factors render such rates particularly unstable.*

[a] Based on number of cases with a report on shock.

[b] Not computed since there were fewer than 10 cases in the sample.

one of the major threats to older persons suffering a myocardial infarction.

Shock at Any Time during the Total Six-Week Period

When shock at any time was analyzed in the same manner as heart failure, shock was also found to have been almost as frequent a symptom as heart failure in this series. Twenty-nine per cent of all patients in the total sample suffered from shock at some time during their illness. In about two-thirds of these cases, shock never exceeded one or two degrees of severity, but in the remaining, the shock experienced was moderate to severe at its maximum point (see Table 71, Appendix F Table 26, and Figure 71). Age trends for shock present a sharp contrast to those for heart failure as Table 72, Appendix F Table 26, and Figure 72 demonstrate. In the case of shock, no clear increase with age was noted in the total proportion of persons who experienced shock following their myocardial infarction; however, among those who did develop shock, its severity increased noticeably with age. *The hazard associated with age in myocardial infarction cases appears, therefore, to be one of increased intensity of shock symptoms rather than of an increased likelihood of its occurrence.*

A somewhat lower percentage of the treated group than of the control group suffered from shock at some time during their illness (27 per cent, treated, *vs.* 30 per cent, control). This fact suggests that anticoagulant therapy may have given this group some slight advantage, especially since analysis indicates that the difference was created mostly by a difference during the later weeks which include most of the usual period of therapy (see p. 137). If the rate of development of *new* shock during the second through the sixth week in the treated group is equalized with that in the control group by the same procedure described for

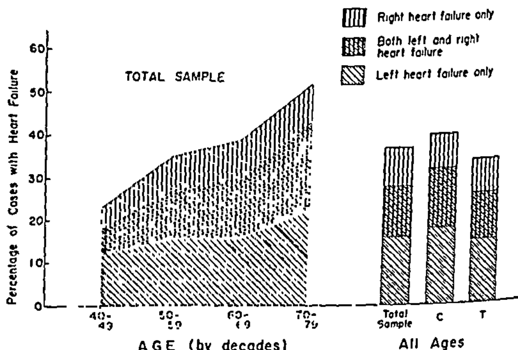


Figure 70. LEFT AND RIGHT HEART FAILURE, BY AGE: Percentage of cases in the total sample showing left or right heart failure, or both at any time during the six-week period of observation, by age, and similar percentages for cases of all ages in the total sample and in the control and treated groups.

sion with myocardial infarction by decade of age was noted by Master, Dack, and Jaffe.[138] These authors reported that among their 500 cases, the percentage of patients in the various age groups who developed heart failure of grades two to four increased from 31 per cent among patients under 40 to 70 per cent among patients 70 to 79. Similarly, pulmonary edema increased from 13 per cent among persons under 40 to 22 per cent among persons in the eighth decade.

Rosenbaum and Levine,[206] Mintz and Katz,[142] and Master, Dack, and Jaffe[138] all found that congestive heart failure occurred somewhat more frequently in women than in men. Master, Dack, and Jaffe also report that pulmonary edema occurred in 15 per cent of their men and 21 per cent of their women. These authors ascribed the greater incidence of congestive heart failure in women to the greater incidence of cardiac enlargement among their female patients. These authors also observed that pulmonary edema, with or without pain, frequently initiated an attack of coronary occlusion with myocardial infarction, especially among women. Mintz and Katz also report a higher average age for women with heart failure than for women in general in their series and a somewhat lesser difference between corresponding averages in the case of men.

Investigators have also noted an association between prolonged arrhythmias of various types and congestive heart failure. Levine and Brown[115] have reported that three-quarters of the cases of myocardial infarction who develop sinus tachycardia also show congestive heart failure. Mintz and Katz[142] found that 48 per cent of 115 patients with sinus tachycardia developed cardiac failure and 71 per cent of these died. Mintz and Katz also observed that 51 per cent of 72 patients with intraventricular block developed congestive heart failure.

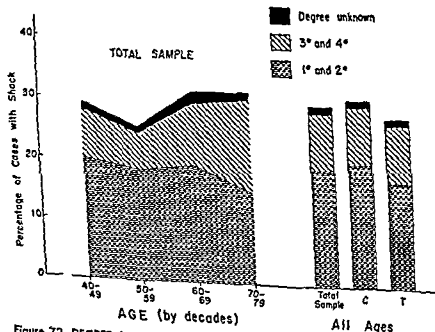


Figure 72. DEGREE OF SHOCK, BY AGE. Percentage of cases in the total sample showing various degrees of shock any time during the six-week period of observation, by age, and similar percentages for cases of all ages in the total sample and in the control and treated groups.

age appear in Appendix F Table 26 for those who wish to make further comparisons of severity by age subgroups.

Heart Failure as Reported in Other Series

The incidence of congestive heart failure complicating coronary occlusion with myocardial infarction as reported by various observers varies widely, due in part to the differences in the clinical material studied and in part to the different criteria used for the designation of this syndrome. This variation is apparent in Table 73. Most of the figures relate to the total illness rather than to initial symptoms. The effect of the type of sample on the rates found is well illustrated by the low proportion of cases with congestive failure in the series of Yater et al.[245]. Since they studied only men under 40 years of age, all of whom had at one time been able to qualify physically for army service, and since only a small proportion of their fatal cases survived to the second day of hospitalization, very low congestive failure rates were to be expected.

Mintz and Katz[152] emphasize that it is difficult to assess the significance of congestive heart failure complicating coronary occlusion with myocardial infarction since many patients exhibiting heart failure also present symptoms and signs of shock, as reported by Fishberg,[59] Harrison,[77] Master, Dack, and Jaffe,[144] and others. These observers agree that the prognosis for cases with congestive heart failure is grave. Harrison, however, emphasizes that this may vary, depending upon the cause of the congestive failure. In fatal cases in whom death is delayed, the symptoms of congestive heart failure predominate. The findings of various authors and of the present study with respect to prognosis are discussed in Chapter XI.

An increasing incidence of congestive heart failure complicating coronary occlu-

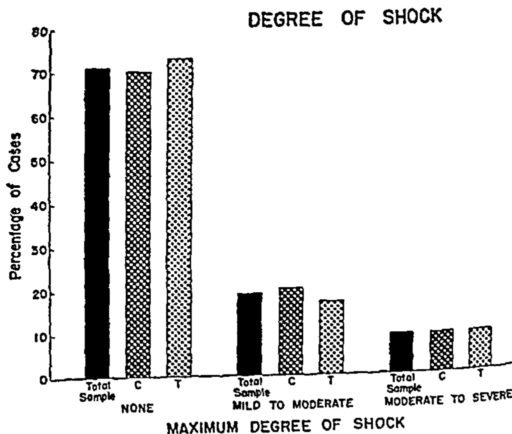


Figure 71. DEGREE OF SHOCK: Percentage of cases in the total sample and in the control and treated groups showing maximum shock of various degrees during the six-week period of observation.

was compared with the normal range for the particular hospital reporting the case.

In 5 per cent of those cases for whom a sedimentation rate was reported, the maximum rate did not at any time exceed the normal range. Since many of these patients lacked reports for part of their period of illness, the true proportion without elevation would clearly have been lower with full reporting. An elevated sedimentation rate sometime during the illness is thus nearly universal in definitely diagnosed myocardial infarction cases surviving beyond the initial period following the attack.

As shown by the data tabulated in Table 75 (based on Appendix F, Table 27), as presented graphically in Figure 73, and as tested statistically, there was no significant difference between the percentage of cases in the control and in the treated groups exhibiting elevated sedimentation rates (1) during the entire six-week period of observation, (2) during the first week of the illness, or (3) during the second through the sixth week. The percentages of cases exhibiting elevated sedimentation rates were definitely higher in later weeks than in the first. As indicated by Table 75, there was apparently little difference between younger and older patients in the percentages with known elevation of the sedimentation rate.

No attempt was made to analyze the time of onset or the duration of the accelerated sedimentation rate since determinations were performed too infrequently and too inconsistently to permit valid comparisons between significant numbers of cases. Analysis of the degree of elevation on an interhospital basis was further handicapped by the great variety of methods of determination and hence of meanings of given elevations in different hospitals. These limitations greatly restricted possible analyses of this measure.

It is common knowledge that the erythrocyte sedimentation rate ordinarily becomes accelerated following an acute coronary occlusion with myocardial infarction. The evolution of the changes in the sedimentation rate has both diagnostic and prognostic value. In not all series of cases of coronary occlusion with myocardial infarction have the percentages of patients with an accelerated sedimentation rate been as high as in the present series. For example, Yater et al.[114] found that the sedimentation rate remained [illegible] of hospital [illegible] of acute m[illegible] infarction whose records were analyzed in this respect. Tredway[222]

TABLE 74

OCCURRENCE OF SHOCK IN SEVERAL [illegible]

Author(s)	Number of Cases Observed	Cases Developing Shock	
		Number of Cases	Percentage of Cases
This series:			
As initial symptom	1031	205	20
At any time[a]	1015[b]	289	29
Rosenbaum & Levine[201]	208	—[c]	54
Bean[14]	300		
First attack		79	57
Second attack		34	45
Yater et al[114]			
Symptom at onset			
Fatal cases	242	90	37
Survivors	400	19	5
Total	642	100	17
Main symptom			
Fatal cases	242	—[d]	—[d]
Survivors	400	30	8
Master, Dack & Jaffe[158]	500	—[c]	53

[a] See footnote a, Table 73

[b] Excluding those in which status of shock was not reported.

[c] Number of cases not reported.

[d] Individual symptoms of shock alone or in combination totaled 313 instances among 242 fatal cases and 436 instances among 400 survivors. The number of cases considered to be in shock is not given for fatal cases and the percentage also is not given.

Many patients presenting an arrhythmia are severely ill and give a history of previous myocardial infarction, cardiac enlargement, heart failure and hypertension. Thus, both cardiac arrhythmias and congestive heart failure are apt to occur in badly damaged hearts and it is difficult to assess the role of the arrhythmia in producing heart failure.

TABLE 73

OCCURRENCE OF CONGESTIVE HEART FAILURE IN SEVERAL SERIES OF MYOCARDIAL INFARCTION: Number and Percentage of Cases Developing Congestive Heart Failure in This Series and in Several Series of Acute Coronary Occlusion with Myocardial Infarction Reported in the Literature

Author(s)	Number of Cases Observed	Cases Developing Heart Failure	
		Number of Cases	Percentage of Cases
This series:			
As initial symptom	1031	219	21
At any time[a]	1031	379	37
Yater et al.[115b]			
Symptom at onset			
Fatal cases	242	5	2
Survivors	400	—	0
Main symptom			
Fatal cases	242	10	4
Survivors	400	0	0
Gross & Engelberg[71]	100	—[c]	90
Mintz & Katz[117]	572	121	23
Males	392	65	17
Females	180	56	31
Master, Dack & Jaffe[133]	500	—[c]	{51[d] 16[d]

[a] Figure probably reflects some influence of anticoagulants in the treated component of the total sample.

[b] Yater's patients were all men younger than 40. The histories were obtained in a very low percentage of fatal cases. Among the 54 patients [illegible] during hospitalization. Twenty-eight developed congestive heart failure subsequent to discharge from the hospital.

[c] Number of cases not reported.

[d] Fifty-one per cent developed frank failure and 16 per cent, pulmonary edema.

Shock as Reported in Other Series

The difficulty of evaluating symptoms which might be attributed to shock has been commented upon by Yater et al.[115] who pointed out that, whereas, among their survivors, individual symptoms of shock were noted 436 times, in only 30 instances was the combination of symptoms and signs such that the attending physician designated the patient to be in a state of "shock."

The incidence of shock following coronary occlusion with myocardial infarction as reported in several series varies considerably. A summary of these rates appears in Table 74.

Master, Dack and Jaffe[133] found the incidence of shock among patients under 40 years (64 per cent) and over 70 (65 per cent) somewhat greater than that among patients in the intervening decades (49 to 55 per cent). They state, however, that they observed only a small number of patients in each of these two more extreme age groups. They also noted that the incidence of shock by sex was roughly comparable, 53 per cent of their males and 52 per cent of their females exhibiting symptoms of shock. They conclude, therefore, that shock occurs in approximately 50 per cent of patients and equally in the two sexes. The observations of various authors with respect to the prognosis in cases showing shock will be covered in Chapter XI, where the findings of the present study in respect to deaths in cases with shock are reported.

LABORATORY OBSERVATIONS DURING THE PRESENT ILLNESS

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate was determined on one or more occasions during the six-week period of observation for 956 of the 1031 patients reported in this study. In each instance, the observed rate

observed that elevations in the sedimentation rate occurred in 80 per cent of the 54 patients reported by him, with no difference in the percentage with elevations between the fatal and nonfatal cases. According to Chambers,[11] the sedimentation rate, which was elevated in 90 per cent of the 100 cases of acute myocardial infarction observed by him, is of assistance in establishing the diagnosis, but the degree of elevation bears no relation to the prognosis. Perhaps the relatively high proportion in the present series with an elevated sedimentation rate is due to the exclusion of doubtful cases from the series and to the omission of early deaths in which opportunity for elevation did not exist.

A greater percentage of sedimentation rates were elevated *after* the first week of the illness (94 per cent) than during the first week (87 per cent). Following acute coronary occlusion with myocardial infarction, the sedimentation rate may *not* become accelerated for a period of *from one to several days.* [illegible] of the sedimentation rate. In instances where such a complication has occurred, both the degree of elevation and its duration may be increased.

The absence of any significant difference in the percentage of patients in the control and treated groups exhibiting elevated sedimentation rates is of interest but is not definitive since the measure used would not reveal some types of differences during the course. It is now well established, however, that the administration of anticoagulants has no influence on the erythrocyte sedimentation rate. *Thus, this rate may be used as a guide to diagnosis and prognosis in* [illegible]

Wright and Prandoni[10] reported in 1942 that dicumarol does not produce an increase in the erythrocyte sedimentation rate. This view was contested by others, notably by Allen, Barker and Waugh,[4] but the Mayo group has subsequently reversed its original stand and now agrees that dicumarol does not accelerate the erythrocyte sedimentation rate.[11] Cosgriff[12] has reported a well-controlled study on patients receiving dicumarol, heparin, or both, in amounts considered to be therapeutic. No significant alteration in the sedimentation rate occurred during the administration of these anticoagulants alone, or in combination. Litwins et al.[13] have confirmed the absence of any influence of dicumarol on the erythrocyte sedimentation rate (1) in patients with normal sedimentation rates, (2) in patients with accelerated sedimentation rates following myocardial infarction, and (3) in patients with accelerated sedimentation rates due to causes other than myocardial infarction. Weir, Eagan and Wolfson[14] have concluded on the basis of their personal observations that an increased sedimentation rate "in any condition being treated with dicumarol is due to the disease state or a complication and not to anticoagulant therapy."

Palmer and Gundersen[15] administered dicumarol to 5 normal males in amounts sufficient to produce a reduction in prothrombin activity to between 10 and 30 per cent of normal and maintained this depression of prothrombin activity for a period of 25 days. The erythrocyte sedimentation rate remained essentially unaltered in all 5 subjects during this period of time. Hyman and Harris[17] gave dicumarol to 10 normal subjects in amounts sufficient to cause a prolongation of the prothrombin time to 25 to 35 seconds (one-stage method of Quick; normal prothrombin time 13 seconds). No significant change occurred in the erythrocyte sedimentation rate which could be attributed to dicumarol.

Quick[18] has reached the same conclusion in experiments performed on normal dogs, while LeRoy and Nalefski[19] confirmed the fact in dogs in whom experimental coronary occlusion with myocardial infarction had

TABLE 75

SEDIMENTATION RATE: Percentage of Cases in the Total Sample and in the Control and Treated Groups with Elevated Sedimentation Rate, by Period of Illness and Broad Age Groups

Period of Illness	Percentage of Cases with Elevated[a] Sedimentation Rate[b]								
	Total Sample			Control Group			Treated Group		
	All Ages[c]	Under 60	60 and Over	All ages[c]	Under 60	60 and Over	All Ages[c]	Under 60	60 and Over
Total six-week period	95	96	93	94	95	93	95	96	94
First week	87	88	86	86	86	86	88	90	86
Second through sixth week	94	93	95	94	94	94	94	93	96
	Number of Cases with at Least One Sedimentation Rate Reported for Period								
Total six-week period	956	527	427	405	218	187	551	309	240
First week	789	443	344	331	182	149	458	261	195
Second through sixth week	802	475	325	343	197	146	459	278	179

[a] Cases were classified as elevated if the maximum rate reported exceeded the range reported as normal for the hospital where the case was treated.

[b] Based on number of cases with at least one sedimentation rate reported for period.

[c] In some cases totals for all ages exceed sum of two subgroups since the subgroups exclude cases of unknown age.

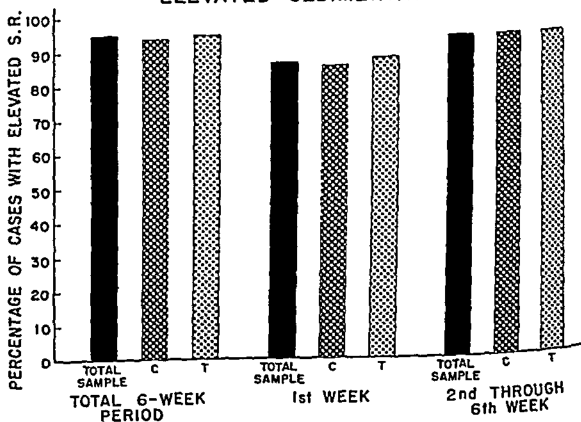


Figure 73. ELEVATED SEDIMENTATION RATE: Percentage of cases in the total sample and in the control and treated groups with an elevated sedimentation rate during various periods of their illness.

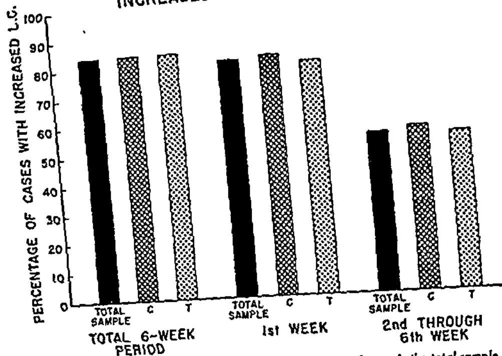


Figure 74. INCREASED LEUKOCYTE COUNT: Percentage of cases in the total sample and in the control and treated groups with an increased leukocyte count during various periods of their illness.

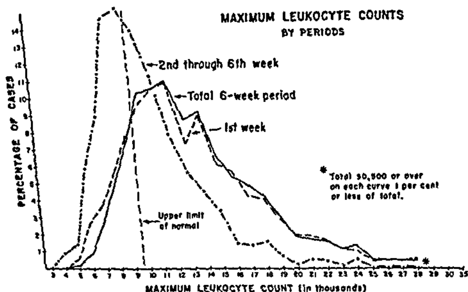


Figure 75. MAXIMUM LEUKOCYTE COUNTS BY PERIODS: Percentage of cases in the total sample reported to have maximum leukocyte counts at various levels during various periods of their illness.

been produced by coronary ligation. Other confirmatory reports have also appeared.

Leukocyte Counts

One or more leukocyte counts were reported for 1027 of the 1031 patients in this series. In each instance the count was compared with a normal range of from 4,500 to 9,400 leukocytes per cubic millimeter. At least one leukocyte count exceeded 9,400 cells per cubic millimeter in 84 per cent of the cases for which one or more counts were reported. With more frequent readings this percentage would doubtless have been higher.

Reference to Table 76 and to Figure 74 shows that there was no apparent difference in the percentage of patients in the control and treated groups exhibiting elevated leukocyte counts (count of 9,500 cells or above per cubic millimeter) over the entire six-week period of observation, the figures being 84 per cent for both groups. When the leukocyte counts during the first week of illness only are considered, the percentage of cases exhibiting elevated counts was 80 per cent for the entire sample, 81 per cent for the control group, and 79 per cent for the treated group. The difference between treatment groups is not statistically significant.

TABLE 76

ELEVATED LEUKOCYTE COUNT: Percentage of Cases in the Total Sample and in the Control and Treated Groups with Elevated Leukocyte Counts, by Period of Illness

Period of Illness	Percentage of Cases with Elevated[a] Leukocyte Count[b]		
	Total Sample	Control Group	Treated Group
Total six-week period......	84	84	84
First week..	80	81	79
Second through sixth week	53	55	52
	Number of Cases with at Least One Leukocyte Count Reported for Period		
Total six-week period .	1027	439	588
First week..	927	395	532
Second through sixth week.	797	338	459

[a] Cases were classified as elevated if their highest reading during the period in question was 9,500 or above (when classified to the nearest 100). Maximums are influenced by the number of readings reported (see footnote[b] of Appendix F Table 28).

[b] Based on number of cases with at least one leukocyte count reported for the period in question. For number of cases with elevated leukocyte count, see Appendix F Table 28, "total above normal range."

When the leukocyte counts determined during later weeks were considered, the percentage of cases exhibiting elevated counts was considerably reduced. Again differences by treatment groups were not significant in a statistical sense. Actual percentages were 53 per cent for the total sample, 55 per cent for the control group, and 52 per cent for the treated group.

As indicated by the distribution curves in Figure 75 and as shown in Appendix F, Table 28, no patient exhibited a consistent leukopenia (counts below 4,500 per cubic millimeter) during the first week of the illness and only 6 patients, or 1 per cent of the entire sample, exhibited leukopenia during later weeks.

The control and treated groups were remarkably similar in the proportion of patients reaching various maximum levels during various periods of their illness as reference to Appendix F, Table 28 will indicate. The distribution for the total sample is also portrayed by periods in Figure 75. The lower level in later weeks is clearly evident

The percentage of cases in the total sample with maximum leukocyte counts at or below given maximum levels fell off rapidly as the count increased. Whereas slightly more than one-half of all cases (52 per cent) exhibited a leukocytosis of at least 12,500 to 13,400 leukocytes per cubic millimeter at one time or another, less than one-quarter of all cases (23 per cent) exhibited a count of more than 16,400 leukocytes. About 11 per cent exhibited a leukocyte count of 19,500 or more

TABLE 77

[illegible] and Percentage [illegible] ie Present [illegible] rction

Maximum Leukocyte Count*	This Series				Chambers' Series*			
	Fatal Cases		Survivors		Fatal Cases		Survivors	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
15,000 or less	96	51	627	75	10	29	50	76
15,001-20,000	54	29	156	18	12	35	12	18
20,001-25,000	21	11	43	5	5	15	4	6
Above 25,000	17	9	13	2	7	21	—	—
Total cases with leukocyte counts reported	188	100	839	100	34	100	66	100

* To secure comparability with Chambers' series, class intervals in this table differ from those used in other leukocyte tables

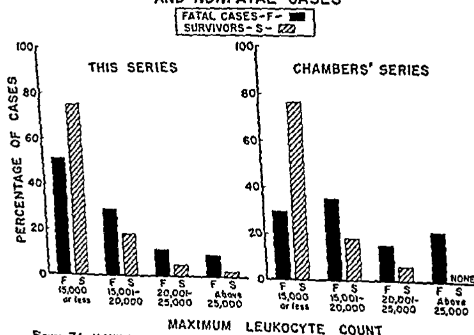


Figure 76. MAXIMUM LEUKOCYTE COUNTS OF FATAL AND NONFATAL CASES: Percentage of cases with maximum leukocyte counts at various levels among fatal cases and survivors in the present series and in Chambers'[41] series of 100 cases of myocardial infarction.

and about 6 per cent exhibited a count of 22,500 or more. Less than 1 per cent of all cases exhibited a leukocytosis of 30,500 or more during the course of observation.

These findings are not unexpected. It is recognized generally that leukocytosis follows promptly most instances of coronary occlusion with myocardial infarction, with both a relative and an absolute increase in the number of polymorphonuclear cells. Ordinarily, leukocytosis appears within a matter of hours, or within one or two days following infarction. The degree of leukocytosis and its duration are thought to be related to the size and location of the infarcted area and are thus of prognostic import. The return of the leukocyte count to normal may be prompt, a matter of a few days, or it may be delayed for as long as several weeks. A secondary rise may indicate any one of many complications, not uncommonly a thromboembolic episode. *There has never been any evidence, as far as we are aware, that anticoagulant therapy modifies the evolution of the leukocytosis which usually occurs following the original infarction, except insofar as thromboembolic complications with subsequent secondary rises in the leukocyte count are prevented.*

Among the 400 survivors in the cases studied by Yater et al.,[265] leukocyte counts were evaluated in 274 patients. The counts remained within normal limits during the entire period of observation in 55 of these 274 patients. Maximum leukocyte counts ranged from 9,000 to 10,000 cells per cubic millimeter in 38 patients, from 11,000 to 19,000 cells in 163 patients, and exceeded 19,000 cells in 18 patients. The leukocyte count reached a maximum within 24 hours following the onset of the attack in 69 per cent of Yater's patients, during the second day, in 15 per cent, and from the third to the eleventh day, in 16 per cent. Eighty-three per cent of the counts had returned to normal within 12 days of the onset of the attack, the others after two weeks, but usually before the end of the third week. The curves of rise and decline of the leukocyte count were similar irrespective of the degree to which the counts were elevated.

Tredway,[237] in comparing fatal and nonfatal cases of coronary occlusion with myocardial infarction in a small series of 54 patients, found average initial leukocyte counts of 16,180 among the survivors and of 15,000 among the fatal cases. The average percentage of polymorphonuclear neutrophils among the survivors was 77 per cent (range of 49 to 94 per cent) while among the fatal cases it was 82 per cent (range from 71 to 91 per cent).

Chambers[41] found that the leukocyte count is both of diagnostic and prognostic value. The leukocyte count was elevated in 90 per cent of the 34 fatal cases and in 70 per cent of the 66 nonfatal cases observed by him. The average leukocyte count among the fatal cases was 20,000 cells per cubic millimeter; it was 13,000 among the nonfatal cases. The relation of the outcome of the observed attack to the leukocyte count in Chambers' series of 100 cases is shown by Table 77 and Figure 76 and is there compared with data from the present series tabulated in similar categories. The close similarity in the distribution of maximum leukocyte counts of survivors in the two series is striking. Among the fatal cases the similarity is less close, the readings for fatal cases in the present series being less elevated. The difference between the two series is probably due either to chance factors or more probably to the exclusion in the present series of cases dying within 24 hours of hospitalization, a procedure which would be expected to eliminate a few cases with very high counts. *Apparently the leukocyte count has some prognostic value, particularly in the high ranges. Counts above 20,000 cells per cubic millimeter are especially associated with a very high mortality.*

low 13.0 grams exhibited erythrocyte counts of 5.6 million cells or more.

Distribution curves for erythrocyte counts and for hemoglobin levels appear as Figures 78 and 79. There is no striking deviation from a smooth curve in either instance. These findings do not confirm the original claims of Klein[103] that an elevated hemoglobin is found in the majority of cases of coronary thrombosis, but do confirm the findings of Keating et al.[t]

TABLE 79

HEMOGLOBIN READINGS: Number and Percentage of First Hemoglobin Readings Following Infarction Falling at Various Levels among Two Hundred Cases Admitted to The New York Hospital with Coronary Thrombosis with Myocardial Infarction[a]

Level of First Hemoglobin Reading after the Attack (in gms)	Cases of Coronary Thrombosis with Myocardial Infarction[b]	
	Number	Per Cent
Below 13 0:		
5.0–5.9	1	.5
6.0–6.9	1	.5
7.0–7.9	—	—
8 0–8.9	1	.5
9.0–9.9	1	.5
10.0–10.9	2	1.0
11.0–11.9	7	3.5
12.0–12.9	10	5.0
Total below 13 0	23	11.5
In range 13.0–15 9:		
13.0–13.9	31	15.5
14.0–14.9	58	29.0
15.0–15.9	49	24.5
Total in range 13 0–15.9	138	69.0
16 0 and above:		
16 0–16 9	27	13.5
17 0–17.9	6	3.0
18.0–18.9	5	2 5
19 0–19.9	—	—
20 0–20.9	—	—
21 0–21.9	—	—
22.0–22 9	—	—
	1	5
Total 16.0 and above . .	39	19 5
Total cases	200	100 0

[a] Source: Unpublished data collected by Dr. Grafton E Burke

[b] Each count represents a different case except that one patient readmitted after 6 years with a new attack is counted as a new case Readings ... are omitted.

Polycythemia

The course of polycythemia, whether primary (polycythemia rubra vera, Vasquez-Osler disease), or secondary (erythrocytosis), is complicated not uncommonly with vascular episodes which may be either thromboembolic or hemorrhagic. The use of anticoagulants in polycythemia, although indicated from the viewpoint of the tendency to thrombosis, may be associated with a greater danger of hemorrhage than in patients without polycythemia, whether due to the effect of the anticoagulants, or independent of them.

Brown and Giffin[44] found that vascular diseases other than venous thromboses occurred in 27 of 100 cases of polycythemia rubra vera studied by them, and Norman and Allen[144] observed various vascular complications in approximately one-third of their 98 patients with this condition. The vascular disturbances encountered most commonly in polycythemic patients involve the peripheral vessels (arteriosclerosis obliterans, acroparesthesia, erythromelalgia, venous thrombosis, etc.) and the cerebral circulation (cerebral thrombosis or hemorrhage), less often the abdominal vessels (mesenteric occlusions). Epistaxis is common in polycythemic patients and serious hemorrhages may complicate even minor operations.

Secondary polycythemia, or erythrocytosis, is observed commonly in two types of heart disease, in those congenital defects in which there is intermingling of arterial and venous blood (e.g , Tetralogy of Fallot) and in pulmonary heart disease (e.g., chronic cor

[t] Keating, J. *et al.*: Unpublished communication.

Erythrocyte Counts and Hemoglobin Determinations

The participating hospitals were not asked to report erythrocyte counts and hemoglobin determinations since such counts were not considered basic to the study and since it was apparent that a detailed analysis of such observations would not be feasible. The complexity of such an analysis would arise from the number of significant variables which, if not adequately taken into account, would make the interpretation of the results open to serious question.

However, since some have suspected that serious degrees of anemia or significant degrees of polycythemia may contribute to the development of coronary occlusion with myocardial infarction, a supplementary attempt was made to determine if any unusual number of cases of anemia or polycythemia arose in a consecutive series of myocardial infarction. In order to clarify this problem, Burke reviewed records of 200 consecutive cases of coronary occlusion with myocardial infarction entering The New York Hospital.* The first reading following the attack was analyzed in each case irrespective of the type of treatment, or whether or not anticoagulant therapy was given.

Comparisons were made on the basis of the following arbitrary divisions for which, it is to be emphasized, the terms "normal" and "abnormal" are not to be specifically assigned, nor are the groupings to be considered necessarily comparable:

Erythrocyte Count	*Hemoglobin Concentration*
0 –3.9 million	0 –12.9 grams
4.0–5.5 million	13.0–15.9 grams
5.6–7.5 million	16.0–22.9 grams

As shown in Table 78 and in Figure 77, 73.5 per cent of the 200 first erythrocyte counts were within the range of 4.0 to 5.5 million cells inclusive. Nine per cent were below 4.0 million cells and 17.5 per cent, 5.6 million cells or above. Similarly, as shown in Table 79 and Figure 77, 69 per cent of the first hemoglobin levels were from 13.0 to 15.9 grams, while 11.5 per cent were below 13 grams and 19.5 per cent, 16.0 grams or more. No cases with erythrocyte counts below 4.0 million cells exhibited hemoglobin levels of 16.0 grams or more, while, conversely, no cases with hemoglobin levels be-

* Burke, Grafton E.: Unpublished data furnished by author.

TABLE 78

ERYTHROCYTE COUNTS: Number and Percentage of First Erythrocyte Counts Following Infarction Falling at Various Levels among Two Hundred Cases Admitted to The New York Hospital with Coronary Thrombosis with Myocardial Infarction[a]

Level of First Erythrocyte Count after the Attack	Cases of Coronary Thrombosis with Myocardial Infarction[b] Number	Per Cent
Below 4.0:		
2.4–2.7	2	1.0
2.8–3.1	2	1.0
3.2–3.5	6	3.0
3.6–3.9	8	4.0
Total below 4.0 ...	18	9.0
In range 4.0–5.5:		
4.0–4.3	25	12.5
4.4–4.7	39	19.5
4.8–5.1	45	22.5
5.2–5.5	38	19.0
Total in range 4.0–5.5 ..	147	73.5
5.6 and over:		
5.6–5.9	19	9.5
6.0–6.3	13	6.5
6.4–6.7	2	1.0
6.8–7.1	1	.5
Total 5.6 and over ...	35	17.5
Total cases ..	200	100.0

[a] Source: Unpublished data collected by Dr. Grafton E. Burke.

[b] Each count represents a different case except that one patient readmitted after 6 years with a new attack is counted as a new case. Readings after extensions are omitted.

findings and the course of the illness in any patient for whom the diagnosis of polycythemia was entertained. On this basis, five patients were reported as exhibiting polycythemia during their period of hospitalization for the current attack of coronary occlusion with myocardial infarction. So small a number of cases precludes analysis, but summaries of the findings are included in Appendix F, Table 29 for their possible interest. Four of these five patients received dicumarol for periods of time ranging from 11 to 40 days without bleeding except in one instance where a slough was present and required surgical intervention.

Blood Cholesterol

This study was begun and, in fact, largely completed before the full development of the current deluge of studies on atherosclerosis and the relation thereto of blood lipid levels and ratios, lipoproteins, macromolecules, etc. Furthermore, it would not have been feasible to have extended the observations required from the participating hospitals in these directions to any important degree. The only relevant observation requested was the determination of the blood cholesterol level. The findings are reported without assigning them any particular importance in the current debate as to what is and what is not significant in the development of atherosclerosis and coronary artery disease.

In this analysis, the definitions of the normal range presented a problem. The figures quoted in the medical literature as representing the upper and the lower limits of normal values for the total cholesterol content of the blood (in mg. per cent of serum

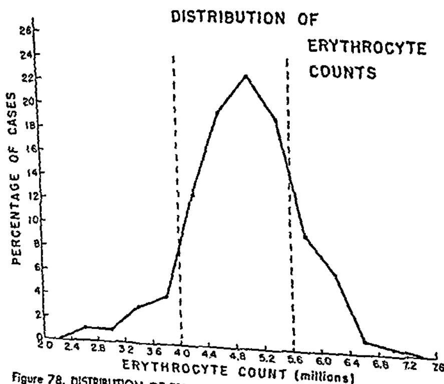


Figure 78. DISTRIBUTION OF ERYTHROCYTE COUNTS: Percentage distribution of first erythrocyte counts following infarction for two hundred cases admitted to The New York Hospital with coronary thrombosis with myocardial infarction.

pulmonale resulting from emphysema, silicosis, etc.). Polycythemia arises occasionally in various types of acquired heart disease, but this is not usual and the changes are not as a rule so pronounced as they are in erythrocytosis secondary to congenital or pulmonary heart disease.

From time to time the question is raised as to the joint incidence of polycythemia and coronary artery disease, more particularly coronary occlusion with myocardial infarction. The impression gained from the literature is that patients with polycythemia do not develop coronary thrombosis with the same frequency with which they are prone to develop other types of vascular complications. For example, in the series reported by Norman and Allen,[166] coronary thrombosis occurred in only two instances, although approximately one-third of the 98 patients developed vascular complications of one sort or another.

On the other hand, patients with coronary artery disease who develop congestive heart failure and dehydration not uncommonly demonstrate an increased erythrocyte count, an elevated hemoglobin concentration and an elevated hematocrit, as shown by Burke's findings[e] that 17.5 per cent of his 200 patients had erythrocyte counts of 5.6 million cells per cubic mm. or above, and 19.5 per cent had hemoglobin levels of 16.0 grams or more. These patients do not usually exhibit the stigmata of true polycythemia—an increased circulating blood volume, an increased number of polymorphonuclear leukocytes and an increased number of platelets. Furthermore, the arterial unsaturation which is characteristic of congestive heart failure and dehydration is not a feature of true polycythemia.

A specific request was made to the participating hospitals to report in some detail the

[e] See footnote e, p. 154.

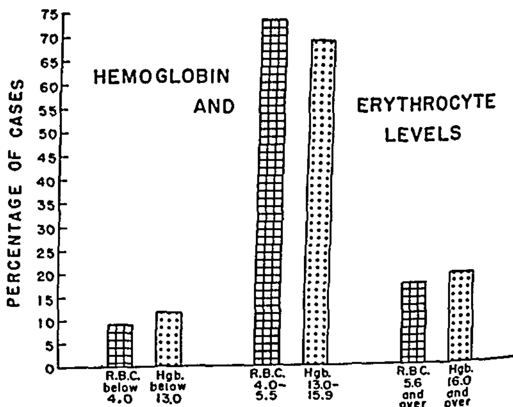


Figure 77. HEMOGLOBIN AND ERYTHROCYTE LEVELS: Percentage of cases among two hundred admissions with coronary thrombosis with myocardial infarction at The New York Hospital with hemoglobin and erythrocyte counts within various ranges following infarction.

10 per cent for the total sample, 9 per cent for the control group and 11 per cent for the treated group.

Fifty-eight per cent of all the cholesterol readings reported were within the normal range for the hospital reporting. Among cases in the control and treated groups, the corresponding percentages were 62 and 55 per cent respectively. When only one blood cholesterol reading, chosen at random, was considered for each case, the percentage of readings within the normal range for the *hospital* reporting was 63 per cent for the

readings were *above* the normal range for the hospital reporting. Among cases in the control and treated groups, the percentages were 25 and 35 per cent respectively. When only one blood cholesterol reading, chosen at random, was considered for each case, the percentages of readings above the normal range for the hospital reporting were, for the total sample, 27 per cent, and for the control and treated groups, 21 and 31 per cent respectively. These percentages are shown graphically in Figure 80.

The differences between the control and treated groups in the percentage elevated were of borderline significance statistically whether one or more than one reading was used. Since there were readings for less than half the total cases, and test and test *norms* differed from hospital to hospital, these differences may be meaningless. If they have

TABLE 80

CHOLESTEROL LEVELS IN ... erol
Readings below Normal, N ...
Control and Treated Grou ... per Case

Cholesterol Reading[a] Level in Relation to Normal Range for Hospital Reporting	All Readings Reported			One Reading per Case (Chosen at Random)[b]		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
	Number of Readings					
Below normal	68	32	36	46	16	30
Within normal range	361	154	207	288	130	158
Above normal	195	63	132	122	39	83
Total readings	624	249	375	456	185	271
Total cases	1031	442	589	1031	442	589
	Percentage of Readings					
Below normal	11	13	10	10	9	11
Within normal range	58	62	55	63	70	58
Above normal	31	25	35	27	21	31
Total readings	100	100	100	100	100	100

[a] Report form asked for maximum reading for given day (or week). Tests were done by the individual hospitals by a great variety of methods with a corresponding variety in ... These ranges were taken into account in the classification of ...

[b] When more than one readi... group and 72 in the treated gr... order not to introduce a select...

[c] Based on total number of ... treatment group.

or plasma) vary widely, a variation which is explained only in part by the difference in the methods used for the determination of cholesterol. Textbooks and manuals of clinical pathology usually cite a figure somewhere between 100 and 150 mg. per cent for the lower limit of normal values and a figure somewhere between 250 and 325 mg. per cent for the upper limit of normal values.

The evaluation of the cholesterol levels in this study was complicated further by the fact that several methods and a number of modifications of these methods for determining the total cholesterol content of the blood were employed by the various participating hospitals. The ranges of values accepted as normal by the respective hospitals varied considerably; the lower limit of normal, from 109 to 200 mg. per cent; the upper limit of normal, from 190 to 330 mg. per cent. The method employed for the determination of the total cholesterol level of the blood in each participating hospital and the range of values considered to represent the normal range for the total blood cholesterol by each hospital appear in Appendix F, Table 30.

The blood cholesterol level was determined at least once for 456 patients of the 1031 observed in this study. More than one such determination was made per patient during the period of observation in 110 cases.

When the blood cholesterol values reported for individual patients were compared with the range of normal values for blood cholesterol reported by the hospital in which the particular patient was studied, the data summarized in Table 80 were obtained. Eleven per cent of all readings reported were below the normal range for the hospital reporting. Among cases in the control and treated groups, the corresponding percentages were 13 and 10 per cent respectively. When only one blood cholesterol reading, chosen at random, was considered for each case, the percentage of readings below the normal range for the hospital reporting was

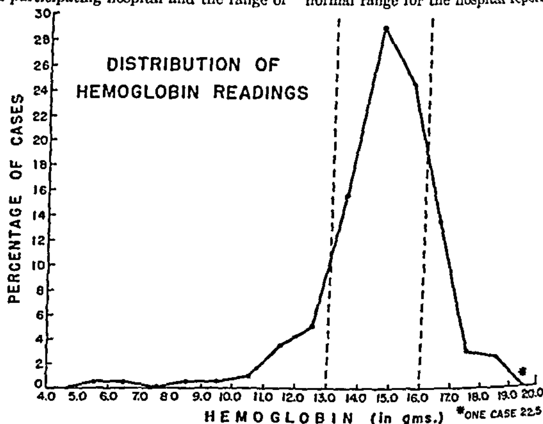


Figure 79. DISTRIBUTION OF HEMOGLOBIN READINGS: *Percentage distribution of first hemoglobin readings following infarction for two hundred cases admitted to The New York Hospital with coronary thrombosis with myocardial infarction.*

TABLE 81

ACTUAL CHOLESTEROL LEVELS: Number and Percentage of Cholesterol Readings at Various Specific Levels Reported for the Total Sample among All Readings Reported and for One Reading per Case

Cholesterol Level[a]	Number of Readings: All Reported Readings	Number of Readings: One Reading per Case (Chosen at Random)[b]	Percentage of Readings: All Reported Readings	Percentage of Readings: One Reading per Case (Chosen at Random)[b]
80–99	7	2	1.1	.4
100–119	16	10	2.6	2.2
120–139	42	32	6.7	7.0
140–159	50	37	8.0	8.1
160–179	62	53	9.9	11.6
180–199	73	49	11.7	10.8
200–219	72	55	11.5	12.1
220–239	74	52	11.9	11.4
240–259	48	32	7.7	7.0
Total under 260	444	322	71.2	70.6
260–279	45	38	7.2	8.4
280–299	39	29	6.2	6.4
300–319	26	16	4.1	3.5
320–339	22	13	3.5	2.9
340–359	10	9	1.6	2 0
360–379	13	12	2.1	2.6
380–399	5	5	.8	1.1
400–419	5	5	.8	1.1
420–439	2	1	.3	.2
440–459	5	2	.8	.4
460–479	1	—	.2	—
480–499	3	2	.5	.4
500–519	2	1	.3	.2
. .	—	—	—	—
620–639	1	—	2	—
	—	—	—	—
660–679	1	1	.2	.2
Total 260 or over[c]	180	134	28.8	29.4
Total readings	624	456	100.0	100.0

[a] See footnote a, Table 80.

[b] See footnote b, Table 80.

[c] The typical (or modal) normal maximum was 250. Seven cooperating hospitals reported normal maximums over 260; nine, below 260.

hours following hospital admission, and subsequently in a large percentage of cases at intervals of two to six weeks. Thirty presumably normal individuals and 36 patients with a variety of diseases were studied similarly as controls. The blood cholesterol levels were within the range of 150 to 260 mg. per cent in all but one of the normal subjects (97 per cent). The distribution among subjects with miscellaneous diseases corresponded closely to that of the series of presumably normal persons, except for 5 instances above the normal range in all of which there were diseases known to be associated with disturbance of cholesterol metabolism. The distribution of cholesterol values among the patients who had suffered acute coronary occlusions was distinctly abnormal. When the cases were analyzed according to age, it was shown that 68 per cent of 75 patients who were less than sixty years of age and 48 per cent of 125 patients who were more than sixty years of age exhibited elevated cholesterol levels. When it was calculated at what average age acute coronary thrombosis would occur in groups having different levels of blood cholesterol, it was apparent that coronary occlusion occurs earlier in life in those persons who exhibit high blood cholesterol values.

Yater and his co-workers[111] found among their young men that, when the normal range for cholesterol values was 150 *to* 250 mg. per cent, the levels among patients during or shortly after an acute attack of coronary occlusion were normal in 43 instances and elevated in 23 instances, or in approximately 35 per cent of their patients, a prevalence of hypercholesterolemia of only one-half that observed in patients under 60 by Morrison, Hall, and Chaney *but* closely comparable to the findings in this study in which adults of all ages were pooled.

Azotemia (*Uremia*)

The reporting of azotemia was inconsistent since the instructions did not stress this point, nor did the reporting forms include a

any meaning, they may be presumed to exert an unfavorable rather than a favorable influence on prognosis for the treated group.

The number and percentage of cholesterol readings at various specific levels for cases in the total sample are summarized in Table 81. Using the data for one reading per case, 60 per cent of readings were 200 mg. per cent, or above. Thereafter, the percentages fell off rapidly with each increment. Only 15 per cent of readings were 300 mg. per cent, or above, and only 3 per cent of readings were 400 mg. per cent, or above.

Morrison and Johnson[154] have studied the level of cholesterol and its esters in the blood serum of persons who have died of acute coronary artery thrombosis and of others who have died of other and unrelated causes. They reported that hypercholesterolemia was found in most of a small group of the patients who died of acute coronary artery thrombosis (average blood cholesterol in 11 patients dying of acute coronary thrombosis was 303 mg. per cent), but not among a small comparable control group (average blood cholesterol in 14 persons who had died of causes other than coronary thrombosis was 183 mg. per cent). The average cholesterol content of the coronary arteries in this small group of patients dying of acute coronary thrombosis was four times as great as the average cholesterol content of the coronary arteries in the comparable small group of control patients.

Morrison, Hall and Chaney[153] determined the level of cholesterol and cholesterol esters in the blood of 200 unselected and consecutive cases of acute coronary thrombosis. Blood cholesterol levels were determined by the Sperry-Schoenheimer method within 48

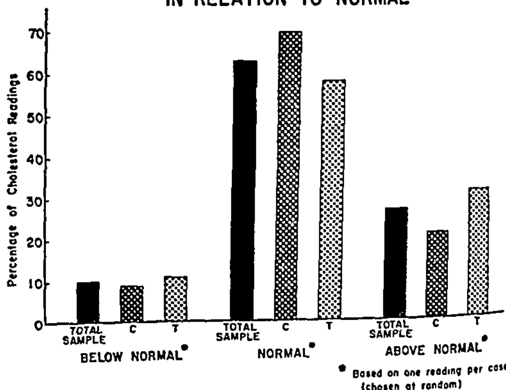


Figure 80. CHOLESTEROL LEVELS IN RELATION TO NORMAL: Percentage of cholesterol readings below and within normal range and above normal among cases in the total sample and in the control and treated groups with a report on cholesterol level (normality determined by relation to normal range for hospital reporting).

TABLE 81

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420-439	2	1	.3	.2
440-459	5	2	.8	.4
460-479	1	—	2	—
480-499	3	2	.5	.4
500-519	2	1	.3	.2
	—	—	—	—
620-639	1	—	.2	—
	—	—	—	—
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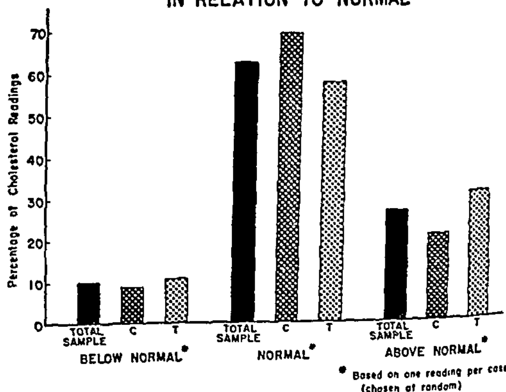


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to inadequate reporting. In view of the lack of consistent reports of nonprotein nitrogen and blood urea nitrogen findings by dates, further analysis of azotemia in the present series was not attempted.

The blood nonprotein nitrogen and the blood urea nitrogen are not uncommonly elevated following a coronary occlusion with myocardial infarction, especially in the presence of congestive heart failure or peripheral circulatory failure. In many instances there are intrinsic renal lesions, such as in nephrosclerosis, which may not have been sufficiently extensive to produce azotemia until complicated by the additional circulatory disturbance If the intrinsic renal involvement is not severe, the azotemia tends to disappear as the circulatory disturbances subside.

The explanation usually advanced for this transient azotemia is that nitrogen retention develops after [illegible] gen is thus most apt to accompany the unfavorable prognostic signs of hypotension and circulatory failure. In the absence of severe, irreversible renal damage, a reversal of azotemia may occur and is a favorable prognostic sign.

Yater et al.[163] observed that among the survivors in their series of relatively young men suffering a coronary occlusion with myocardial infarction, the nonprotein nitrogen or blood urea nitrogen was elevated in only 5 of the 55 patients on whom it was determined. Although the nonprotein nitrogens ranged from 45 to 92 mg. per cent in these five subjects immediately following [illegible] period of hospital observation.

Tredway[illegible] found an elevation of the blood urea nitrogen in 8 of his 21 fatal cases of coronary occlusion with myocardial infarction, with an average value of 21.1 mg. per cent. There was an elevation of the blood urea nitrogen in 7 of the 33 survivors, with an average blood urea nitrogen of 20.9 mg. per cent. Among the patients with elevated blood urea nitrogens in the group of survivors, the only two with "abnormally high blood urea nitrogens" died within 9 months. Thus both the incidence and the levels of the elevated blood urea nitrogens were slightly higher in the fatal than in the nonfatal cases.

MISCELLANEOUS COMPLICATIONS

Diseases of the Various Body Systems Observed during the Present Illness

As anticipated among patients predominantly of middle or advanced age, many in the present series suffered from one or more complicating diseases or conditions related only remotely or not at all to their coronary artery disease. The list of these miscellaneous and diverse conditions is long (see Appendix F, Table 31). Even this list is undoubtedly incomplete since the conditions reported depended upon the care with which the individual patient was studied and the case reported. The majority of the complications so reported did not influence the outcome of the present illness and only rarely had any prognostic significance. When tabulated, as in Appendix F, Table 31, their diversity is more striking than is the incidence of any particular complication.

The conditions most commonly reported are shown in Figure 81. Diabetes mellitus, which was present during the illness period in 10 per cent of the total sample, ranks first in frequency. This condition has been discussed on pages 52-55. The second most common complication reported was azotemia (uremia) which has been discussed on the preceding pages. When pneumonias of all types and locations were placed in a single category, they proved to be the third most common complication, being specifically reported in approximately 5 per cent of all cases. Peptic ulcers, including gastric, prepyloric and duodenal ulcers were [illegible]

section devoted specifically to the matter. *For this reason, observations on individual patients varied widely.* A statement concerning the presence or absence of azotemia was made usually only when uremia was strongly suspected, or was a conspicuous complication of the illness.

The data reported are summarized in Table 82. Among the patients in the total sample, a diagnosis of uremia, or laboratory data on nonprotein nitrogen or blood urea nitrogen findings, or both, indicated that azotemia existed, or probably existed in 7 per cent of the total sample. Half of these cases were classed as "definite azotemia" from the record, using laboratory data where reported, and half as "questionable." There was no significant difference between the control and treated groups in this respect, 7 per cent of the former and 6 per cent of the latter being azotemic. There appears, therefore, to be no evidence of a direct relation of this condition to anticoagulant therapy.

As shown in Table 82, azotemia was most frequently found in fatal cases. Fourteen per cent of the fatal cases showed azotemia, 11 per cent being definitely azotemic and an additional 3 per cent, questionable. In contrast, only 5 per cent of the nonfatal cases were reported as having azotemia and of these, more than half were questionable.

A breakdown by age, also shown in Table 82, fails to show any great difference in the incidence of azotemia in patients under 60 and those 60 and over, except in fatal cases. Among fatal cases, the frequency of azotemia appears to be higher under 60. This difference could be due either to chance or

TABLE 82

AZOTEMIA: Number and Percentage of Cases in the Total Sample Reported as Being Azotemic at Any Time during the Six-Week Period of Observation, by Broad Age Groups and by Fatal or Nonfatal Outcome

Outcome of Case and Age Group	Number of Cases in Total Sample	Number of Cases with Azotemia			Percentage of Cases with Azotemia[b]		
		Total, Any Degree	Definite[a]	Questionable[a]	Total, Any Degree	Definite[a]	Questionable[a]
Fatal cases:							
Under 60	61	12	10	2	20	17	3
60 and over	129	15	12	3	12	9	3
All ages	190	27	22	5	14	11	3
Nonfatal cases:							
Under 60	501	28	9	19	6	2	4
60 and over	337	15	4	11	4	1	3
All ages	841[c]	43	13	30	5	1	4
All cases:							
Under 60	562	40	19	21	7	3	4
60 and over	466	30	16	14	6	3	3
All ages	1031[c]	70	35	35	7	3	4

[a] When laboratory data were reported, cases with maximum NPN readings above 50 or maximum BUN readings above 25 were classed as definite, and those with maximum NPN readings from 30 to 50 or maximum BUN readings of 20 to 25 were classed as questionable. Otherwise, hospital indication of severity, if any, was followed, the "mild" cases being placed in the "questionable" category.

[b] Based on totals in each age and outcome subgroup.

[c] Includes cases of unknown age not included in age subgroups.

in only 4 instances despite a specific inquiry about it.

Cerebral conditions were numerous and varied. Many of these undoubtedly represented reactions to the cerebral anoxia which accompanies hypotension and circulatory failure at the onset of acute myocardial infarction. The others, for the most part, can probably be attributed to cerebrovascular arteriosclerosis, accidents, and their sequelae. A few may have been based on drug toxicity, but, if so, these were not recognized as such.

Patients were reported as anemic in only 9 instances. Polycythemia was specified in only 5 instances. These findings are discussed in some detail on pages 155-157. Diseases of the skin were few and varied. They are discussed briefly on page 167 and in Table 84, since some were suspected of being reactions to medication.

The occurrence of the rheumatic states, particularly of osteoarthritis, was undoubtedly grossly underreported since the latter is present in a high percentage of all persons over 50. Other conditions involving the musculoskeletal system were not reported in any significant numbers. Miscellaneous conditions not limited to a particular body system occurred in 6 persons considered to be alcoholic and 10 patients for whom a diagnosis of syphilis was made. The latter were largely instances of asymptomatic syphilis with a positive blood serology.

Surgical Operations during Period of Observation

Seven surgical operations were performed on patients in this series during the first six weeks after onset (see Table 83). Four of these were performed for thromboembolic complications of the illness: an embolectomy for an embolus developing in the right axillary artery; a supracondylar amputation for a popliteal embolus; and two prophylactic femoral vein ligations, one bilateral, for venous thromboses. Operations on 3 other patients were undertaken during the six-

TABLE 83

OPERATIONS DURING THE ILLNESS: Details regarding Operations Performed Immediately Preceding or during Course of Present Illness

Type of Case	Description
Operations during Course of Present Illness	
Control Group	
Female, age 64	This control patient developed a renal infarct on the 9th day of the illness and was then placed on dicumarol at the request of the private physician. Dosage, however, was reported as "never adequate." On the 22nd day of the illness, patient developed a venous thrombosis of the right calf and suffered a pulmonary embolus. A bilateral superficial femoral vein ligation was performed on the same day.
Male, age 47	This control patient developed a thrombophlebitis on the 17th day of the illness. A femoral ligation was performed on the same day and dicumarol was given on this day and on the day following.
Male, age 56	This control patient suffered an embolus to the right axillary artery on the 7th day of the illness. Heparin was given on the following day but was discontinued after one day. An embolectomy was performed on the following (8th) day. A pulmonary embolus occurred on the 10th day and heparin and dicumarol were given thereafter.
Male, age 62	A right nephrectomy was performed for a papillary cystadenoma and chronic pyelonephritis on the 41st day of the illness. There were no complications.

previous cholecystectomy was reported to have been observed in more than 1 per cent of all cases. There was no great difference in the prevalence of these more common complications in the control and treated groups (see Figure 81).

Cardiovascular conditions other than pericarditis, hypertension, congestive heart failure, arteriosclerosis and coronary artery disease previously discussed were reported in only 8 instances. These included the following: 3 instances of rheumatic heart disease; 2, of syphilitic heart disease; 1, of subacute bacterial endocarditis; and 2, of aneurysms.

When the pneumonias and acute upper respiratory infections are omitted, the diseases of the respiratory system fall into two distinct categories: bronchial afflictions and diseases involving the lungs and pleura. The former include bronchitis, bronchiectasis and asthma, but it is not clear that bronchial and cardiac asthma were always clearly differentiated. There was no significant number of any one of the conditions involving the lungs or the pleura.

Except for peptic ulcer, specific disorders involving the stomach and intestines were present only in insignificant numbers. Jaundice was reported in 7 instances, but the etiology was not specified in any case. Of 13 instances of liver disease, the cause was not recorded in 8. Twelve patients had gallbladder disease, while 20 patients had previously undergone cholecystectomy.

There were many instances of renal and urinary tract disease, as might be anticipated from the ages of the patients in this series, but no great number were described as having any single condition.

Except for diabetes mellitus, discussed previously, the recognized diseases of metabolism were largely those of the thyroid gland. In only 3 instances was gout listed as currently present during the illness. It will be recalled that a history of gout was reported

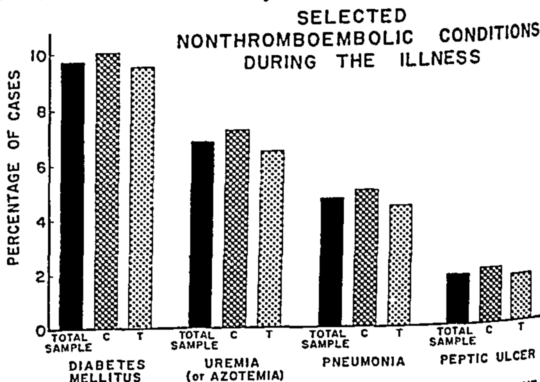


Figure 81. SELECTED NONTHROMBOEMBOLIC CONDITIONS DURING THE ILLNESS: Percentage of cases in the total sample and in the control and treated groups for whom the six-week period of illness observed was complicated by selected nonthromboembolic conditions.

Cutaneous Eruptions

Although complications other than hemorrhage have rarely been attributed to the use of the anticoagulants clinically, there have been occasional reports of immediate or delayed hypersensitivity reactions in patients receiving anticoagulants which have been thought due to these agents. True anaphylactic reactions to heparin were reported from the Scandinavian countries during the early use of that agent, but these have usually been ascribed to impurities in the preparations since they have not been reported after the introduction of more highly purified products. Toxic reactions of a delayed nature, occurring from one to two hours after the injection of heparin and characterized by chills, fever, headache and lumbar backache, are probably of similar origin. Sorenson, Seifter and Wright[314] have reported that several patients showed immediate toxic reactions following intravenous injection of Paritol, a synthetic polysulfuric acid ester of polyanhydromannuronic acid similar to heparin in both chemical structure and action.[b] The most severe reaction, a shock-like phenomenon, included nausea, vomiting, abdominal cramps, defecation, precordial oppression, sweating, bradycardia and a fall in blood pressure to imperceptible levels. These signs and symptoms responded promptly to the administration of epinephrine. Milder reactions in other cases included flushing of the face, edema of the hands, gastrointestinal distress, and a modest fall in the blood pressure. The manifestations disappeared promptly when injection of Paritol was discontinued.

Skin rashes of various types, but usually erythematous, have been described uncommonly in patients receiving dicumarol, but in most instances the patients have been

that dicumarol played any role in the cutaneous manifestation. Allen, Barker and Hines[4] have reported the unusual occurrence of urticaria during dicumarol therapy, possibly a hypersensitivity reaction to this agent.

Because of the possibility that sensitivity reactions to heparin or dicumarol might be encountered in a series of this magnitude, all dermatological manifestations reported were reviewed to assess the role of anticoagulants in their production. During the period of observation, cutaneous eruptions were reported as appearing in 8 instances, 6 among patients who received anticoagulants (1.0 per cent of this group) and 2, among patients who received no anticoagulants (0.5 per cent of this group). The essential information concerning each of these eruptions is summarized in Table 84. Unfortunately, for a clear assessment of the role of anticoagulants, each of these patients was receiving from 2 to as many as 6 therapeutic agents in addition to the anticoagulant. In most instances there were one or several drugs being administered which are notorious in the production of dermatitis.

The greater number of cutaneous eruptions among patients receiving anticoagulants than among those not receiving this therapy may have been due to (1) chance, (2) the slightly greater percentage of the treated group receiving such agents as narcotics, hypnotics (barbiturates, bromides, chloral hydrate), salicylates and quinidine (see Table 88, Chapter VII), all of which are known to produce cutaneous reactions not uncommonly, and (3) alertness of both patients and physicians for the appearance of cutaneous lesions in patients receiving anticoagulants because of the possibility of hemorrhagic manifestations arising from this therapy. *In no case could it be concluded that a cutaneous eruption was definitely due to anticoagulants and in only one case was a cutaneous eruption even considered to be possibly related to anticoagulant therapy.*

TABLE 83 (cont.)

Type of Case	Description
Male, unknown age	This control patient was admitted with marked icterus and right upper quadrant pain. Diagnoses of common duct stone with ascending cholangitis and of small anterior myocardial infarction were made. Cholecystostomy and choledochoduodenostomy were performed on the 13th day of the illness and cholecystostomy tubes were removed on the 25th day.
Male, age 68	This control patient developed a popliteal embolus on the 21st day of the illness and was started on heparin and dicumarol on the 25th day of the illness because of this complication. A right supracondylar amputation was performed on the 39th day. Prothrombin time on day of operation was 23 seconds. Dicumarol was continued to the 45th day.
Female, age 56	This control patient with polycythemia developed a pulmonary embolus and was placed on dicumarol. Dicumarol was discontinued on the 24th day to permit the surgical closure of a slough which had occurred following a hypodermoclysis in the skin and soft tissues of the thigh. Bleeding occurred postoperatively at the site of operation.
Operations Shortly before Attack	
Treated Group	
Male, age 88	This patient entered the hospital on GU service because of gross hematuria of 36 hours duration. Calculi were found in the bladder. The patient then developed an incarceration of a right femoral hernia A right femoral hernia repair and cystoscopy were performed. Patient developed an acute coronary occlusion with myocardial infarction on the 3rd postoperative day. Although a treated group case, patient was not given anticoagulants because they were considered to be contraindicated.
Male, age 52	A bilateral ligation and stripping of varicose veins was performed for this patient on the same day as the onset of his coronary attack.
Male, age 56	This patient, hospitalized for 20 days, had a left ureterectomy for pyoureter (nephrectomy 22 years previously). Attack of acute coronary occlusion with myocardial infarction occurred on same day. Patient was placed on dicumarol on the 6th day following the coronary occlusion.

week observation period: a nephrectomy for papillary cystadenoma and chronic pyelonephritis (on 41st day); a cholecystostomy and choledochoduedenostomy for a common duct stone with ascending cholangitis (on 13th day); and the debridement of a slough.

In two other instances the original myocardial infarction occurred on the same day as an operation (see Table 26, Chapter V); in one instance, following a bilateral ligation and stripping of varicose veins; in another, following an ureterectomy for pyoureter. A third patient suffered his acute coronary occlusion with myocardial infarction on the third postoperative day following a right femoral hernioplasty and cystoscopy.

Cutaneous Eruptions

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Skin rashes of various types, but usually erythematous, have been described uncommonly in patients receiving dicumarol, but in most instances the patients have been receiving one or more other therapeutic agents and it is impossible to state with certainty that dicumarol played any role in the cutaneous manifestation. Allen, Barker and Hines[3] have reported the unusual occurrence of urticaria during dicumarol therapy, possibly a hypersensitivity reaction to this agent.

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[b] For additional reports on this anticoagulant, see Seifter and Begany,[illegible] Sorenson and Wright,[324] Marple and Wright,[illegible] pp. 281-283, and Wright.[illegible]

COMPARISON OF THE CONTROL AND TREATED GROUPS USING MULTIPLE CRITERIA

The presentation thus far has concentrated on the comparison of the control and treated groups using one characteristic or symptom at a time, or, at most, age and sex, plus one characteristic. Schnur[314] has suggested the use of a composite index for such comparisons in order to facilitate the simul-

TABLE 84

RASHES: Details Regarding Rashes Occurring during Present Illness and Their Relation to Anticoagulant Therapy

Type of Rash	Day of Dicumarol Therapy[a]	Total Dose of Dicumarol (in mg.)[a]	Other Drugs during Illness	Remarks
Cases Receiving Anticoagulants[b]				
Erythema nodosa	9	600	Patient received papaverine, 0 6 gm , and morphine, 0.6 gm., daily.	Erythematous nodules developed on the leg and were thought to be erythema nodosa. No interpretation of cause.
Multiforme erythema	16	950	Patient had been receiving morphine, codeine, phenobarbital and chloral hydrate.	All medication withdrawn upon rapid onset of arthralgia and erythema multiforme (of skin and mucous membrane), considered a drug sensitivity to chloral hydrate
Maculopapular eruption	10	1200	Patient had been receiving morphine, demerol, atropine, salicylates and barbiturates.	Rash appeared on flexor surfaces of arms and legs, fluctuating in severity and disappearing and reappearing while on dicumarol Skin test with dicumarol was negative; rash thought not due to dicumarol.
Skin rash (type not specified)	14	1550	Patient had been receiving demerol, papaverine, salicylates, bromides, and barbiturates.	Rash thought due to bromides.
Rash (type not specified)	18	1650	Patient had been receiving morphine, demerol, atropine, xanthines, barbiturates and chloral hydrate.	Pruritic rash over trunk and arms for one week, cause not determined; probably not due to dicumarol.
Rash (type not specified)	12	1500	Patient had been receiving quinidine, 1 6 gm. and penicillin (total of 750,000 units).	Undescribed rash, reported due to penicillin.

[a] Including day rash first observed.
[b] Treated group included one case each of furniculosis and of psoriasis.

TABLE 84 (cont.)

Type of Rash	Day of Dicumarol Therapy[a]	Total Dose of Dicumarol (in mg.)[a]	Other Drugs during Illness	Remarks
Cases Receiving No Anticoagulants				
Rash (type not specified)	No dicumarol	—	Patient had been receiving morphine, codeine, papaverine, salicylates, barbiturates and penicillin.	Dermatitis medicamentosus, pruritic, cause not determined, duration approximately 9 days. Penicillin given to patient for 3 days but stopped because of rash. Treated with benadryl.
Rash (type not specified)	No dicumarol	—	Patient had been receiving mercurial diuretics, 22 cc., sodium phenobarbital, .13 gm I.M., and penicillin ophthalmic ointment.	Dermatitis medicamentosus, generalized, cause not determined.

taneous consideration of many traits. For this purpose he has proposed the use of a pathologic index rating (P. I. R.). The procedure provides for scoring each case for unfavorable prognostic signs according to a standardized, though somewhat arbitrary, rating system that includes both items from the patient's history and selected conditions present on admission.[i] While his proposed scoring system does not accord fully with the findings of the present study as to what constitute significant prognostic signs,[j] the procedure was nevertheless applied to the cases in the present study as an additional test of comparability.

Fortunately, it was possible to find data in the records for the present study that were approximately comparable in coverage to those utilized by Schnur and to define the procedures for scoring so that an uneven application of the procedure to the control and treated groups was impossible.[k] On this basis, the average P. I. R. for the total control and total treated group was found to be as follows:

Control group	44
Treated group	43

Both averages fall in the lower portion of the range of 40 to 59 characterized by Schnur as corresponding roughly with the clinical classification "moderately severe." For individual patients with all degrees of severity, the index has a range of zero to about 140. In view of the approximate nature of the scor-

[i] The topics considered in this index include shock, congestive heart failure, selected serious arrhythmias, gallop rhythm, diabetes, uremia, urinary tract infection, emphysema, cerebral thrombosis, and a history of hypertension, cardiac enlargement, angina, and previous coronary occlusion.

[j] The index fails to take into account the following conditions found in the present study to be associated with a poor prognosis: heart block, excessive weight, large initial drops in blood pressure, very high leukocyte counts, and marked temperature rises. On the other hand, the index included occasional ventricular contractions and anginal syndrome, conditions not found in the present study to be of any great significance in prognosis.

[k] Where the scoring procedure permitted a choice of score within specified limits for certain conditions, the average score [illegible]

ing procedure, the wide possible range of variation, and the numerous important items omitted from the index, the difference between the control and treated groups seems clearly insignificant. In Schnur's graph relating the mortality rate to the pathologic index rating, an increase of one point in the P. I. R. was associated, at the levels between 30 and 50 P. I. R., with an increase of only about one-half of one per cent in the death rate. The observed difference in P. I. R. is thus clearly inadequate to explain the observed difference in total deaths (23.4 per cent, control *vs.* 16.0 per cent, treated).

The fact that both these P. I. R. averages were higher than those found by Schnur for patients with a fatality rate similar to that for the control group in the present study is probably not significant. This higher level is doubtless related to (1) the completeness of the recording, reporting, and coding of the history and conditions on admission in the present study and (2) to the somewhat more inclusive definitions used in the present study for some of the categories involved in the index.[1] *This analysis involving multiple criteria thus yields further evidence that the control and treated groups were comparable with respect to the types of cases included.* The application of these criteria is, however, not to be considered as an endorsement of Schnur's P. I. R.—which, while of interest in principle, is inadequate in numerous respects since it omits items of importance and overemphasizes other items of lesser significance. It, therefore, cannot be relied on for the comprehensive evaluation of comparability in a study of this nature.

[1] For example, with available data as coded, it was not feasible to limit scores for the arrhythmias to manifestations of the patient's status at the time of admission, the first week being used as a substitute. Difficulties of a similar type were presented by a few other categories. For this reason it is possible that the average score for the treated group was slightly reduced by the influence of

however, when such a scoring system is used, it is important that only symptoms and conditions that have occurred so early that they cannot be influenced by therapy be included; otherwise, the results of a given type of therapy will be reflected in part in a lower P. I. R instead of in lower case fatality rates for given P. I. R. levels.

SUMMARY AND CONCLUSIONS RELATIVE TO THE COURSE OF THE ILLNESS (SUMMARY OF CHAPTER V AND CHAPTER VI)

Validity of Diagnosis

The data on signs, symptoms and laboratory findings in the first week were originally collected as supporting evidence for the original diagnosis of myocardial infarction. The validity of the diagnoses could be confirmed in all but a few cases by electrocardiographic evidence since the attending physicians had, in all except two cases, at least one electrocardiogram for reference. For the great majority of cases, several electrocardiograms were available. These were utilized to localize the infarction in all but 23 cases where the location of the infarction was obscured by bundle branch block or other such conditions and 50 cases in which the changes were described as diffuse. That the diagnosis of an infarction thus arrived at was correct in a remarkably high percentage of cases is suggested by the fact that of 91 cases that came to necropsy, a myocardial infarction was demonstrated in 89, or 98 per cent, of such cases. *It is therefore clear that the sample studied constituted, in fact, a series of patients with myocardial infarction.*

Characteristics of the First Week of the Illness

In view of this finding, the resulting data may be used with confidence to describe the frequency with which the clinical signs, symptoms and laboratory findings of myocardial infarction are found among cases of this type *severe enough to be recognized and hospitalized and yet not so severe as to die*

prior to hospitalization or on the first day after admission. For this purpose, the symptoms of the first week are the most suitable because (1) they are most intense and dramatic at this time, (2) they are relatively uninfluenced by anticoagulant therapy, and (3) they are reported more fully for this period than for later weeks.

A convenient summary picture for the first week is given in Figure 82 and Table 85, which present the percentage of cases showing various signs, symptoms and laboratory findings during the first week among all those with a report on the items in question. *Six were reported as occurring in four-fifths or more of the total sample:* (1) *pain of typical location,* (2) *a drop in blood pressure,* (3) *elevation of temperature to 100° or more, rectal,* (4) *an elevation of sedimentation rate above normal limits,* (5) *elevated pulse rate* (*90* per *minute or more*), and (6) *elevated leukocyte count* (*9,500 or more*). *All six are clearly related to the basic process of infarction and with frequent and more precise determination might have been found practically universal.*

The remaining signs, symptoms and laboratory findings tabulated reflect for the most part varying degrees and kinds of cardiac damage resulting from the infarction or from the infarction superimposed on prior cardiac damage. They were therefore much less universal than those that reflect the process as such. *In descending order of frequency of reporting, these were: dyspnea* (*48 per cent*), *cardiac enlargement* (*41 per cent*), *abnormal heart rhythms* (*36 per cent*), *vomiting* (*29 per cent*), *shock* (*26 per cent*), *left heart failure* (*24* per *cent*), *right heart failure* (*17 per cent*), *and* [illegible]

right heart failure were specifically: pulmonary edema (23 per cent), liver enlargement (13 per cent), and peripheral edema (8 per cent). The category of abnormal rhythms included auricular fibrillation and left or right bundle branch block, each of

SIGNS, SYMPTOMS, AND LABORATORY FINDINGS
IN THE FIRST WEEK

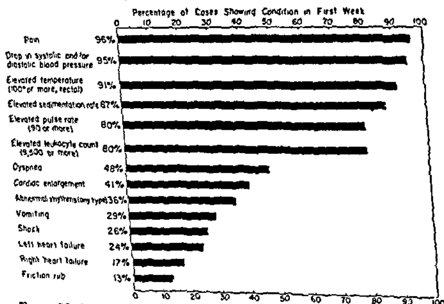


Figure 82. SIGNS, SYMPTOMS, AND LABORATORY FINDINGS IN THE FIRST WEEK: Percentage of cases in the total sample with a report on a given sign, symptom or laboratory finding who showed selected conditions during the first week following the onset of their attack.

ing procedure, the wide possible range of variation, and the numerous important items omitted from the index, the difference between the control and treated groups seems cl[illegible] relating [illegible] index rating, an increase of one point in the P. I. R. was associated, at the levels between 30 and 50 P. I. R., with an increase of only about one-half of one per cent in the death rate. The observed difference in P. I. R. is thus clearly inadequate to explain the observed difference in total deaths (23.4 per cent, control *vs.* 16.0 per cent, treated).

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[1] For example, with available data as coded, it was not feasible to limit scores for the arrhythmias to manifestations of the patient's status at the time of admission, the first week being used as a substitute. Difficulties of a similar type were presented by a few other categories. For this reason it is possible that the average score for the treated group was slightly reduced by the influence of early anticoagulant therapy. In this instance the conclusions regarding the effectiveness of therapy are obvious in spite of this possibility; in general, however, when such a scoring system is used, it is important that only symptoms and conditions that have occurred so early that they cannot be influenced by therapy be included; otherwise, the results of a given type of therapy will be reflected in part in a lower P. I. R. instead of in lower case fatality rates for given P. I. R. levels.

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The pattern with respect to the direction of differences was also well balanced except for five comparisons that concerned various symptoms of heart failure (see Table 85) and were in one sense repeated measures of the same basic phenomenon. In all five indices of heart failure within the first-week period, the control group was slightly higher than the treated group, although never to the point of statistical significance. Much of this difference involved initial heart failure only. Because the counts involved repeated counts of various manifestations of the same syndrome in the same patients, the observed consistency would be expected and should not be given undue weight in evaluating the overall balance between the control and treated groups[m] In heart failure persisting

[m] The minor differences present perhaps reflect a hesitancy on the part of a few physicians to use anticoagulants when congestive heart failure was present as an initial symptom. If the percentage

TABLE 85

[illegible] Characteristics within the First Week of the Illness

Type of Sign, Symptom, or Laboratory Finding	Percentage of Cases[a] Showing Given Characteristic within First Week[b]		
	Total Sample	Control Group	Treated Group
Characteristics in which treated group was higher than control group:			
Illness severe at onset	29	26	31
Initial shock	20	19	20
Pain, any degree	96	95 (.7)	96 (.3)
[illegible]	80	79	81
[illegible]	95	94	95
[illegible]	87	86	88
[illegible]	13	11	14
Characteristics in which treated group was lower than control group:			
A. Characteristics other than congestive heart failure			
Shock, any degree	26	27	26
Elevated leukocyte count (9,500, or more)	80	81	79
Maximum temperature 100.0° or more, rectal	91	92	90
Cardiac enlargement, any degree	41	45	38
Dyspnea, any degree	43	51	47
Abnormal rhythms, any type	36	37	35
Vomiting	29	30	28
Gallop rhythm	6	7	6
B. Various indications of congestive heart failure			
Initial heart failure, any degree	21	24	19
Heart failure, any degree	31	33	29
Liver enlargement, any degree	13	16	12
Pulmonary edema, any degree	23	26	21
Peripheral edema, any degree	8	[illegible]	[illegible]

[a] Percentages [illegible] teristic [illegible] sample e[illegible] the base [illegible]

[b] Cou[illegible] on occurrences any time during first week except where words "initial" or "onset" appear in the stub. [illegible] Appendix F tables relevant to the subject in question. [illegible] Actual numbers in [illegible]

which were observed during the first week in 7 per cent of the cases. Gallop rhythm was observed in 6 per cent. Other common symptoms such as ashen gray color, cold clammy hands, sweating, and apprehension were not analyzed statistically.

Blood cholesterol levels were not tabulated specifically for the first week but rather from a random selection of all readings for the total period for each case; they were found elevated in 27 per cent of the cases. Records for elevated hemoglobin (16.0 mg. and over) and elevated red cell count (5.6 million or over) were collected for a supplementary series (page 154) rather than for the present one. Elevations above these specified levels were found in one-fifth or less of the cases studied, among whom were a number of cases in congestive failure. Elevations in these readings were therefore not considered a direct characteristic of myocardial infarction.

In addition to tabulation by their symptoms in the first week, patients were classified according to their status at onset and during the first two days. Twenty-nine per cent of the cases were evaluated by the attending physician as severe at onset, 21 per cent showed some degree or type of initial heart failure during the first two days, and 20 per cent developed shock during this same initial period. These percentages may also be considered essentially free of anticoagulant influence and therefore representative of the general level of severity for the series.

Comparisons of these findings with other studies revealed a very wide range in findings from study to study and served to emphasize how greatly findings are influenced by the type of sample utilized and its size, the completeness of reporting, the definitions adopted, and the procedures of analysis. Where rough comparisons were possible, the findings of the present study typically took a somewhat central position midway between the high and low findings of some other studies. These comparisons have therefore served to reinforce and supplement the findings of the present study and to give *further assurance that the sample employed* was typical of hospitalized cases of myocardial infarction of the type the sample was presumed to represent.

Data for the initial period and the first week were also used repeatedly to test the comparability of the control and treated groups with respect to their initial composition prior to any influence by anticoagulant therapy. *Of the many comparisons made, 20 of the most important were tested for the statistical significance of the differences between the control and treated groups. These 20 are listed in Table 85. None of these differences was found statistically significant by the definition adopted for this study (1 per cent significance level)* and only one difference, namely, that for cardiac enlargement, was found of borderline significance (below 5 per cent significance level). Although these tests by their nature cannot offer positive proof of no difference, they do consistently *fail to disprove* at the adopted significance level the hypothesis that the control and treated groups were drawn from the same types of patients. In addition, numerous other percentages and means not tested for significance have also been reported in the text and appendix. Differences between the control and treated groups were routinely minor and apparently random in nature. These untested similarities are well illustrated by the following means for the first week:

	Control Group	Treated Group
Mean maximum blood pressure drop (mms. Hg)		
Systolic	52	51
Diastolic	28	25
Mean maximum pulse (beats per minute)	108	107
Mean maximum temperature (degrees Fahrenheit, rectal)	101.8	101.6

favored the control group since the control group thereby lost prior to this period certain patients with particularly adverse signs and symptoms. Including measures of congestive heart failure, *a total of 18 comparisons were tried and in 16, or all but two, the treated group was found to be the lower, in 13 of the 16 the difference being at least 1 percentile point.* These are listed in Table 86. This increased imbalance with regard to the direction of the difference appears to reflect the indirect effect on signs, symptoms, syndromes and laboratory findings of a reduction in the incidence of thromboembolic complications. Most differences were not striking and none reached statistical significance at the one per cent level. However, two of the differences were large enough so that they would be

TABLE 86

SUMMARY OF SIGNS, SYMPTOMS, AND LABORATORY FINDINGS, SECOND THROUGH SIXTH WEEK: Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Given Characteristics within the Period from the Second through the Sixth Week of the Illness

Type of Sign, Symptom, or Laboratory Finding	Percentage of Survivors at Beginning of Second Week[a] Showing Given Characteristic at Any Time during Second through Sixth Week		
	Total Sample	Control Group	Treated Group
Characteristics in which treated group was higher than control group:			
Maximum pulse, 90 or more	76.5	74.3	78.1
Maximum temperature 100.0° or more, rectal	81.5	79.9	82.8
Characteristics in which treated group was lower than control group:			
A. Characteristics other than congestive heart failure			
Illness severe during course	19.1[b]	21.7[b]	17.1[b]
Shock, any degree	4.5	5.8	3.5
Pain, any degree	19.6	21.7	18.1
Drop in blood pressure below usual level (both systolic and diastolic ...	96.7	96.8	96.6
[illegible]	53.4	55.0	52.3
[illegible]	93.9	94.2	93.7
[illegible]	50.3	54.8	46.9
[illegible]	12.9	15.8	10.8
[illegible]	26.3	28.6	24.6
[illegible]	1.5	2.2	.9
...riction rub	2.4	3.0	2.0
Gallop rhythm	3.5	3.6	3.4
B. Various indications of congestive heart failure			
Heart failure, any degree	19.2	21.5	17.7
Liver enlargement, any degree	9.9	11.4	8.8
Pulmonary edema, any degree	13.0	14.4	12.0
Peripheral edema, any degree	5.1	[illegible]	[illegible]

[a] Percentages for ... teristi... charac... pressu... record... Apper... relevant to the subject in question. ... in the bases in each case can be ascertained from ... extent apparent from the

[b] Percentages differ from those previously reported since they refer only to survivors at the beginning of the second week rather than to all cases in the sample.

into the second week and not obviously related to complications, the two treatment groups were at the same level, namely, 13 per cent of all cases surviving to the second week. It is therefore doubtful that this transient difference with respect to initial heart failure had a significant influence on the experiment. Each of the other 15 tests concerned a different characteristic. In these, the control group was the higher in 8 and the treated group, in 7. (The percentages compared in these tests are listed in Table 85.) Moreover, the observed differences were never substantial.

In addition to these comparisons of various characteristics singly, Schnur's pathologic index rating[214] which involves multiple criteria of severity was computed for the control and treated groups as precisely as the data permitted. These index ratings averaged 44 for the control group and 43 for the treated group. In view of the small difference and the approximate nature of the procedures and data involved, the difference between treatment groups was again clearly insignificant.

It may therefore be concluded that at the outset of the study and during the first week, before anticoagulants could have exerted much effect, differences between the characteristics of the control and treated groups were of minor and mixed character and did not exceed the confidence limits for expected chance differences as defined for this study.[a] *There is no reason to believe that such minor differences as did exist significantly affected the major outcomes under study.*

Course of the Illness after the First Week

After the first week, when the acute symptoms of onset had subsided, a lower proportion of patients than in the first week showed most of the various adverse signs and symptoms. An elevated sedimentation rate, a reduction in blood pressure below usual levels, and an enlarged heart were the only symptoms studied that were more nearly universal in the later period than in the first week. The most dramatic reduction was observed in the proportion experiencing pain. While pain in the first week was nearly universal, only about a fifth of the patients showed any pain at all during later weeks and those who did usually experienced pain of lesser degree than in the first week. Many other symptoms also showed conspicuous reductions in the proportion exhibiting them.

For the present study the particular value of the data for the second through sixth week lies in the opportunity to observe which adverse signs, symptoms and laboratory findings, if any, differed in relation to anticoagulant therapy, for anticoagulants were usually not in full effect until after the first week following the onset of the attack. Comparisons for later weeks were somewhat handicapped by unknowns and possible underreporting for certain symptom categories for those weeks, and by changes affecting the comparability between the two groups as a result of the progressive loss through death of more patients from the control than from the treated group. Comparisons are nevertheless appropriate since it is reasonable to assume that the unknowns were impartially distributed between the two groups and that the loss of severely ill patients through death

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with initial heart failure in the control group had been the same as in the treated group, 23 fewer patients would have shown this syndrome. It is estimated that under these circumstances the percentage of cases dying in the control group would have been about 0 5 per cent less (all other factors remaining equal), a difference which would affect the total picture in only a very minor manner.

[a] No difference exceeded the 1 per cent significance level and only one such difference exceeded the 5 per cent significance level, termed "borderline significance" in this report. The tests used throughout the report minimize the risk of asserting that a difference exists when actually there was no difference between the populations randomly represented by the available samples. For a discussion of the risk of the opposite type of error, namely that of asserting that there is no difference when, in fact, a real and perhaps substantial difference between the populations sampled did exist, see footnote f, p. 59.

during the total six-week period, 10 were favorable to the treated group. Of these, however, only the following four reached borderline statistical significance, namely:

	Percentage of Cases with Condition	
	Control Group	Treated Group
Heart failure, any type	40	34
Cardiac enlargement	51	44
Liver enlargement	19	14
Pulmonary edema	31	24

In 8 of the 10 comparisons favorable to the treated group during the total period, the favorable differential relative to the control group either proportionately increased, or was created for the first time, during the period of effective anticoagulant therapy. Presumably this consistent pattern in the direction of changes from the initial status reflects to some degree the favorable influence of anticoagulants.

Certain other comparisons were made only once for the total period of the illness. Fifty-three per cent of the patients were diagnosed as having infarctions of the anterior type; 37 per cent, infarctions of the posterior type; 1.4 per cent, purely septal infarctions; and 5 per cent, diffuse changes, the remaining being of unknown or multiple site. The most common nonthromboembolic complications of the illness were diabetes (10 per cent), azotemia (7 per cent), and pneumonia (5 per cent). Differences between the control and treated groups in these respects were not [illegible]

[illegible] among 1 per cent of those who received anticoagulants and 0.5 per cent of those who did not. No eruption was definitely attributed to anticoagulants and only one was considered possibly related.

One unexpected difference appeared involving the proportion of patients with an elevated cholesterol level (classified on the basis of one cholesterol reading per case chosen at random). Thirty-one per cent of the treated group as contrasted with 21 per cent of the control group had a cholesterol level that was elevated as defined by the standard of the hospital in question. The difference was of borderline significance statistically. The meaning is obscure. If a true difference of consequence actually existed, which is doubtful, one would suppose that such a difference, if effective at all, would probably have operated to the disadvantage of the treated group.

A number of the symptoms were also studied in relation to age. All symptoms related in some degree to heart failure, namely, cardiac enlargement, pulmonary and peripheral edema, dyspnea, and liver enlargement, showed a definite increase with age as did the syndromes of left and right heart failure The intensity of shock also increased with age. On the other hand, pain, abnormal heart rhythms, vomiting, and friction rub with minor exceptions showed no appreciable tendency to increase with age. These age trends followed similar patterns in both the control and treated groups.

Certain signs and symptoms were also studied in relation to the percentage of cases dying. The following were found associated with a particularly serious *prognosis:* (1) drops in blood pressure of 60 mm. or more, systolic, or 40 mm. or more diastolic (below the usual level prior to the attack) in the first week of the illness, (2) rectal temperatures of 103 degrees or more (Fahrenheit), (3) leukocyte counts of 20,000 or more, and (4) pulse rate maximums of 120 beats per minute or more. Consideration of the relation of the location of infarction, severity at onset, heart failure, shock, and abnormal rhythms to death [illegible] sideratior [illegible] of deaths [illegible]. The remaining symptoms were not analyzed in relation to death rates.

expected on a chance basis less than 3 times in 100, namely, cardiac enlargement (54.8 per cent, control, *vs.* 46.9 per cent, treated) and dyspnea (15.8 per cent, control, *vs.* 10.8 per cent, treated).

In a few instances the data were analyzed to yield a more revealing type of figure, namely, the percentage of survivors at the beginning of the second week who, although they had not shown a given symptom in the first week, developed this symptom sometime during the second through the sixth week. Percentages of this type for congestive heart failure, shock, and cardiac enlargement were as follows:

	Control Group	Treated Group
Congestive heart failure..	11.0	6.0
Shock..	4.4	2.1
Cardiac enlargement	11.8	9.2

The consistently more favorable record for the treated group is again evident.

The data on severity of the course of the illness also suggest that anticoagulants had a favorable influence. While the treated group was higher than the control group in severity at onset (26 per cent severe, control, *vs.* 31 per cent severe, treated), the direction of this difference was reversed during the course of the illness. Twenty-seven per cent of the control group as contrasted with 22 per cent of the treated group showed a severe course. This result was produced by the following changes in severity status: (1) of control patients classified as mildly or moderately ill at onset, 14 per cent developed a severe course, whereas in the treated group only 8 per cent of such patients changed to a severe course (a statistically significant difference);* (2) of control group patients severely ill at onset, 37 per cent showed only a mild or moderate course, whereas in the treated group, 47 per cent of such patients showed a mild or moderate course, though, in this case, the difference was not statistically significant, probably because of the small number of cases involved. Thus a change toward mildness was in evidence in both of these components of the treated group during the course of the illness.

All of these objective findings for the later weeks confirm the reasonable expectation that a reduction in thromboembolic complications as a result of anticoagulant therapy would be reflected in some reduction in adverse symptoms in later weeks. *It therefore seems justifiable to conclude that (1) anticoagulants did not adversely affect the course of the illness in respect to the signs, symptoms and laboratory findings studied, and (2) many adverse symptoms were less frequent in cases protected from thromboembolic complications with anticoagulant therapy than in those not thus protected.* Although evidence for the second of these deductions is not conclusive, it is highly suggestive and remarkably consistent.

Findings for the Total Period Observed

Percentages for the total six-week period have also been reported for most signs, symptoms and laboratory findings. For evaluative purposes these percentages are not, however, satisfactory in all respects since they represent the net effect of (1) procedures in the selection of cases, (2) chance differences, and (3) differences associated with anticoagulant therapy. Rates for the total six-week period were always higher than those for the first week since some patients who did not show specific symptoms in the first week did develop these symptoms in later weeks; however, characteristics that were high in the first week had little chance to be raised further by developments in later weeks. Of 13 comparisons involving the percentage of cases with various signs, symptoms, syndromes, and laboratory findings

* When only those surviving to the beginning of the second week are considered, these percentages become 22 and 17 per cent as quoted in Table 86.

CHAPTER VII

Management of the Illness

THE present chapter reviews and evaluates the available data relative both to the general management of the illness and to the administration of anticoagulants. The text reports in sequence the findings pertinent to length and promptness of hospitalization, types of hospital service received, the proportion of cases receiving some care from a private duty nurse, the drugs administered, miscellaneous aspects of management, and the type and duration of anticoagulant therapy. The information given here on the anticoagulants received is supplemented further in Chapter XII on prothrombin times where the actual doses of anticoagulants used and their effects are considered.

The findings on management here presented serve the triple purpose of (1) characterization of typical hospital management [illegible] ... degree to which the management of patients in the two treatment groups was comparable except for anticoagulant therapy, and (3) determination of the extent to which treated group patients were actually protected by anticoagulants. To be confident that the observed differences in thromboembolic complications and deaths can actually be attributed to anticoagulant therapy, it is obviously necessary not only to establish that the cases included in the two treatment groups were essentially comparable, but also to demonstrate that the management of their illness was similar in all respects except for treatment with anticoagulants.

MANAGEMENT OTHER THAN ANTICOAGULANT THERAPY

Time Spent under Various Conditions of Observation and Care

Comparability of treatment in myocardial infarction is reflected in part in the promptness and duration of hospital care and in time lost to therapy through delays in diagnosis. No particular requirements as to length of hospitalization or time of hospitalization in relation to time of onset were established for the present study. The schedule form did, however, require a report for each patient on the date of onset of the attack, the date of hospitalization, the date of diagnosis, and the date of hospital discharge or death. These facts were reported for all cases in the series although in a few instances where the date of onset was somewhat indeterminate because symptoms developed gradually, the date of onset had to be estimated for statistical purposes. From these reports on dates, the number of days the patients spent under various conditions of observation and care was computed, with the results shown in Appendix F Table 32 and Figure 83. The data reported include by definition only time *within* the six-week period of observation. Since many cases remained in the hospital 8 weeks or longer, inclusion of these longer periods would have increased somewhat the average period of hospitalization.

From computations on this basis, the patients in the sample were found to have spent an average of 29 days in the hospital within the six-week period studied. The treated group averaged 30.0 days and the control

Conclusions

This and the preceding chapter have thus demonstrated a close comparability between the two groups in the signs, symptoms, syndromes, and laboratory findings characterizing the onset of the illness and the first week after the attack before the effective operation of anticoagulant therapy. Chapter IV demonstrated a close similarity in the characteristics of the control and treated groups prior to the attack. There does not, therefore, appear to be any difference between the types of cases in the two groups to which the marked differences in thromboembolic complications and deaths reported in ensuing chapters can be attributed. The present and preceding chapter have reported, in addition, various evidences of minor improvements in the course of the illness in the treated group as compared with the control group that presumably are a reflection of the reduced incidence of thromboembolic complications associated with anticoagulant therapy.

nosed and admitted very late, sometimes only after thromboembolic complications had developed in later weeks. These few cases contributed disproportionately to the averages reported. Nevertheless, the evidence later presented of the large number of thromboembolic complications that developed before anticoagulant therapy was begun or was effective gives silent testimony of the savings that might have been achieved if diagnosis and anticoagulant protection had been more quickly accomplished.

Time prior to hospitalization averaged two and one-half days per case, the figures again being remarkably close for the two groups (2.7 days, control; 2.4 days, treated). Once again the general averages were raised by a relatively few patients who were admitted to the hospital late in their illness. (Admission after the eighth day occurred in 6 6 per cent of the control group and 5 3 per cent of the treated group.) Actually nearly half of the total group (44 per cent) was admitted to the hospital on the day of the attack itself (42.1 per cent, control; 45.7 per cent, treated).

A tendency toward slightly earlier admission for the treated group is evident in all these figures on admission. The difference between treatment groups in the average days prior to the adm [illegible] Nevertheless, the slight differences apparent probably reflect in part (1) the slightly higher proportion of severely ill patients in the treated group and (2) the higher proportion of private patients in this group and the more prompt handling such private patients receive. These differences are discussed further on page 9. Since a difference of 0.3 days (7 hours) in admission time would hardly be sufficient in itself to influence total outcomes for those patients who were able to survive the first 24 hours of hospitalization, one would expect that its effects would be reflected at most only in differences in the composition of the two samples or in the direct effects of anticoagulant therapy on these particular patients, influences which are fully discussed in other chapters.

Time after discharge was also remarkably similar for the two treatment groups (4.8 days, control; 4.7 days, treated). Most of this period for both groups was covered by follow-up contacts. Only 51 patient-days in the total study, or less than one-twentieth of a day per patient, were not covered by a report of some kind concerning fatalities and thromboembolic and hemorrhagic phenomena developing during the postdischarge period but before the end of six weeks.

There is thus no reason to believe that differences in the promptness of admission to the hospital, the time prior to diagnosis, the duration of hospital care, or differences in the extent of follow-up observation influenced the differences in outcomes reported. The reverse did, however, occur. Anticoagulants, by reducing early discharges due to death, did increase the average length of hospitalization slightly.

Type of Hospital and Nursing Service Rendered

Type of Hospital Service.

Data regarding the hospitals in which the patients in this series were treated were reported on pages 24-25. The present section supplements these data with information on ward and private care and nursing service. Participating hospitals were asked to designate whether each patient in the series had been hospitalized on (1) a private service, (2) a semiprivate service, (3) a ward service, or (4) a mixed service (instances where a patient was transferred from one type of service to another). Reporting in this respect was not entirely accurate. Furthermore, one type of service in a given hospital might be comparable to an essentially different type of service in another hospital. The data are presented, however, to give a rough indication of the type of service supplied to the patients. These data are reported in

group, 28.2 days. This difference of 1.8 days was the most obvious revealed by this analysis and is of borderline significance statistically. On first reflection this difference would perhaps suggest that some difference occurred in the treatment received. However, on further check, it proved to be due almost entirely to the more frequent deaths in the control group since such deaths obviously resulted in premature termination of hospitalization. When the averages for days of observation lost within the six-week period because of the death of the patient (6.3 days, control, *vs.* 4.9 days, treated) were added to the averages for days of hospitalization observed, the totals for the two averages became almost identical (34.5 days, control, *vs.* 34.9 days, treated). The very small remaining difference disappeared almost entirely when a further correction was made for the slightly earlier admission of the treated group. *Thus there is no reason to believe that there was any difference between the two groups with respect to the stage of the illness when surviving patients were discharged from the hospital.*

Days prior to diagnosis averaged 2.7 days per case. Averages were again remarkably close for the two groups (2.7 days, control, *vs.* 2.6 days, treated). For the treated group the average number of days prior to the beginning of anticoagulants was 3.9 days. While both these delays were regrettably long, the record for the typical case was considerably better than would appear from these averages since a few cases were diag-

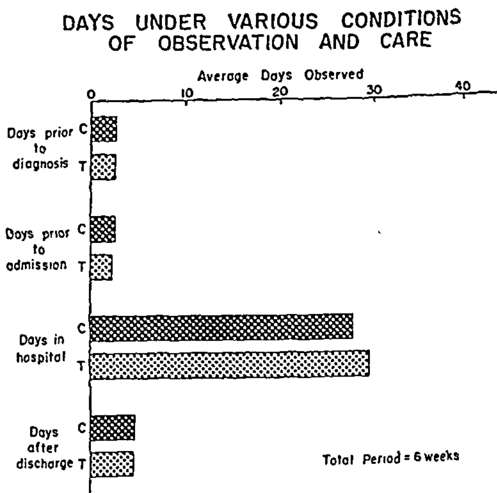


Figure 83. DAYS UNDER VARIOUS CONDITIONS OF OBSERVATION AND CARE: Average number of days spent by patients in the control and treated groups under various conditions of observation and care.

osed and admitted very late, sometimes only after thromboembolic complications had developed in later weeks. These few cases contributed disproportionately to the averages reported. Nevertheless, the evidence later presented of the large number of thromboembolic complications that developed before anticoagulant therapy was begun or was effective gives silent testimony of the savings that might have been achieved if diagnosis and anticoagulant protection had been more quickly accomplished.

Time prior to hospitalization averaged two and one-half days per case, the figures again being remarkably close for the two groups (2.7 days, control; 2.4 days, treated). Once again the general averages were raised by a relatively few patients who were admitted to the hospital late in their illness. (Admission after the eighth day occurred in 6.6 per cent of the control group and 5.3 per cent of the treated group.) Actually nearly half of the total group (44 per cent) was admitted to the hospital on the day of the attack itself (42.1 per cent, control; 45.7 per cent, treated).

A tendency toward slightly earlier admission for the treated group is evident in all these figures on admission. The difference between treatment groups in the average days prior to the admission is not, however, conspicuous graphically (see Figure 83) or statistically significant. Nevertheless, the slight differences apparent probably reflect in part (1) the slightly higher proportion of severely ill patients in the treated group and (2) the higher proportion of private patients in this group and the more prompt handling such private patients receive. These differences are discussed further on page 9. Since a difference of 0.3 days (7 hours) in admission time would hardly be sufficient in itself to influence total outcomes for those patients who were able to survive the first 24 hours of hospitalization, one would expect that its effects would be reflected at most only in differences in the composition of the two samples or in the direct effects of anticoagulant therapy on these particular patients, influences which are fully discussed in other chapters.

Time after discharge was also remarkably similar for the two treatment groups (4.8 days, control; 4.7 days, treated). Most of this period for both groups was covered by follow-up contacts. Only 51 patient-days in the total study, or less than one-twentieth of a day per patient, were not covered by a report of some kind concerning fatalities and thromboembolic and hemorrhagic phenomena developing during the postdischarge period but before the end of six weeks.

There is thus no reason to believe that differences in the promptness of admission to the hospital, the time prior to diagnosis, the duration of hospital care, or differences in the extent of follow-up observation influenced the differences in outcomes reported. The reverse did, however, occur. Anticoagulants, by reducing early discharges due to death, did increase the average length of hospitalization slightly.

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TABLE 87

TYPE OF HOSPITAL SERVICE: Percentage of Cases in the Total Sample and in the Control and Treated Groups Receiving Ward and Private or Semiprivate Care during the First Six Weeks of Observation

Type of Care	Percentage of Cases		
	Total Sample	Control Group	Treated Group
Ward	61.5	64.7	59.1
Private or semiprivate	35.5[b]	33.9	36.7
Two or more types (in sequence)[a]	3.0	1.4	4.2
Total cases	100.0	100.0	100.0
	Number of Cases		
Total cases	1031	442	589

[a] Cases whose type of service changed during the six-week period studied.

[b] Of the total sample, 30.3 per cent received private care and 5.2 per cent, semiprivate care.

Table 87, in Appendix F Table 33 (by hospitals) and in Figure 84.

Of the total number of patients from all hospitals, 61.5 per cent were ward patients, a fact that indicates that the sample represents largely the lower income groups in the population. The percentages for the control and the treated groups were, respectively, 64.7 and 59.1 per cent. This difference is not statistically significant. Thirty-five and five-tenths per cent of the patients in the total sample received private or semiprivate care, while in the control and treated groups the percentages were, respectively, 33.9 and 36.7 per cent. The remaining patients received more than one type of hospital care during the period of observation.

The proportions varied greatly by hospitals (see Appendix F Table 33). At one extreme were seven hospitals that reported that 100 per cent of the patients studied by them were ward patients. At the other ex-

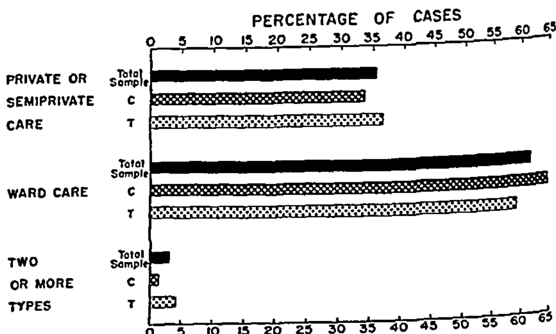


Figure 84. TYPE OF HOSPITAL SERVICE: Percentage of cases in total sample and in the control and treated groups receiving ward or private or semiprivate care, or two or more types of care.

treme was Henry Ford Hospital that reported only private cases. In most hospitals the percentages receiving ward care were approximately similar in the control and treated groups, but in a few hospitals there were substantial differences (see Appendix F, Table 33). In most cases comparisons are meaningless because of the small samples involved.

Type of Nursing Care

In addition to type of hospital service, reports were requested as to whether the patient was cared for at any time by a private duty nurse. Reports of this type were received for all but 36 cases in the control group and 51 cases in the treated group. Tabulation of these reports (see Appendix F, Table 34) indicated that 10 per cent of the total sample received private duty nursing care at some time during their illness. As would be expected, an economic difference in this respect was in evidence, for 22 per cent of the private and semiprivate cases had a private duty nurse as contrasted with 3 per cent of the ward cases. Similarly, the severity of the case influenced the employment of a private nurse. Twenty per cent of patients severely ill at onset had a private nurse as compared with 6 per cent of those appearing only mildly or moderately ill at onset.

Some differences in private duty nursing care were also evident by treatment groups. When all types of hospital service were considered together, 6.9 per cent of the control group as compared with 12.1 per cent of the treated group were found to have had a private duty nurse at some time. This excess occurred primarily in the private and semiprivate care group. For ward care, the more usual type in the present series, the imbalance tended in the opposite direction. Four per cent of the control group ward cases, as compared with 2 per cent of the treated group ward cases, had a private duty nurse. Nevertheless, in the uncorrected form, the difference for the total control and treated groups was very close to statistical significance as defined for this study.[a] However, further exploration revealed that this difference was due in part to two factors: (1) the greater severity at onset in the treated group, and (2) the higher proportion of private and semiprivate cases in the treated group. When these disproportions were artificially equalized, the contrast was reduced. It became 7.5 per cent for the control group and 11.5 per cent for the treated group.[b] In this corrected form the difference in the use of private duty nurses is reduced to a figure clearly only of borderline statistical significance.[c] Therefore, by the definitions adopted for this study, explanation in terms of chance remains possible, even though improbable. Data with which to verify or refute other possible explanations are lacking.[d]

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[a] Differences as great as this occur 1.1 times per 100 on a chance basis.

[b] These [illegible]

[c] The significance tests followed the procedure for such tests for standardized rates described in Appendix C and indicated that a difference of this amount would occur about four times in one hundred on a chance basis.

[d] As reported on page 20, 31 even-day cases received anticoagulants for miscellaneous reasons before the development of a complication, the most frequent being the advice of a private physician. A review of these 31 cases indicated that an excessive proportion received private and semiprivate service and likewise an excessive proportion received the services of a [illegible] The analys[illegible] the treate[illegible] tions note[illegible] were simil[illegible] and nursin[illegible] since maintenance of odd- and even-day procedures undoubtedly were particularly difficult with private patients under the care of private physicians.

TABLE 87

TYPE OF HOSPITAL SERVICE: Percentage of Cases in the Total Sample and in the Control and Treated Groups Receiving Ward and Private or Semiprivate Care during the First Six Weeks of Observation

Type of Care	Percentage of Cases		
	Total Sample	Control Group	Treated Group
Ward	61.5	64.7	59.1
Private or semiprivate	35.5[b]	33.9	36.7
Two or more types (in sequence)[a]	3.0	1.4	4.2
Total cases	100.0	100.0	100.0
	Number of Cases		
Total cases	1031	442	589

[a] Cases whose type of service changed during the six-week period studied.

[b] Of the total sample, 30.3 per cent received private care and 5.2 per cent, semiprivate care.

Table 87, in Appendix F Table 33 (by hospitals) and in Figure 84.

Of the total number of patients from all hospitals, 61.5 per cent were ward patients, a fact that indicates that the sample represents largely the lower income groups in the population. The percentages for the control and the treated groups were, respectively, 64.7 and 59.1 per cent. This difference is not statistically significant. Thirty-five and five-tenths per cent of the patients in the total sample received private or semiprivate care, while in the control and treated groups the percentages were, respectively, 33.9 and 36.7 per cent. The remaining patients received more than one type of hospital care during the period of observation.

The proportions varied greatly by hospitals (see Appendix F Table 33). At one extreme were seven hospitals that reported that 100 per cent of the patients studied by them were ward patients. At the other ex-

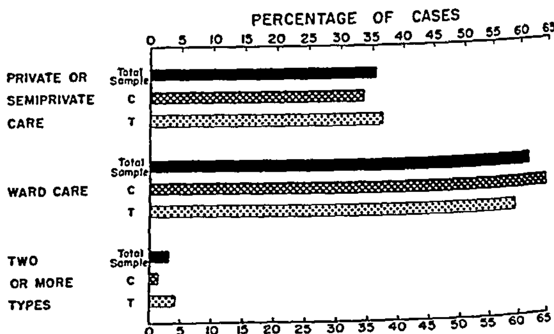


Figure 84. TYPE OF HOSPITAL SERVICE: Percentage of cases in total sample and in the control and treated groups receiving ward or private or semiprivate care, or two or more types of care.

TABLE 88 (cont.)

Type of Drug	Percentage of Cases Receiving Drugs[b]		
	Total Sample	Control Group	Treated Group
Washed erythrocytes ..	.2	.5	0.0
Plasma..............	2 0	2.3	1.9
Total blood and blood substances	3.2[c]	2.7[c]	3.6[c]
Cathartics[d].. . . .	1.6	2.0	1.4
Sympathomimetic drugs	1.3	1.1	1.4
Rutin.	.7	.7	.7
Vitamin C. . .	.7	.2	1.0
Coramine	.5	.2	.7
	Number of Cases		
Total cases	1031	442	589

dosage schedules except in the case of anticoagulants (see Chapter XII). Since, with several exceptions, the form did not require a report of the purpose of a prescription or the dates when it was used, analysis of the purpose and duration of therapy with given drugs was not feasible. Tabulations, therefore, pertain only to the number or percentage of patients receiving each type. The drugs are listed and discussed in descending order according to the proportion of patients receiving them.

Narcotics, essential for the relief of pain and anxiety, were used with more patients than any other drug, being received by nearly two-thirds of all cases. Oxygen, valued for its power to relieve restlessness, dyspnea and pain, ranked next to narcotics in frequency of use. Fifty-seven per cent of all patients received oxygen in some form (tent, mask, or nasal catheter).

Atropine and other antispasmodics (belladonna, syntropan, etc.) were received by

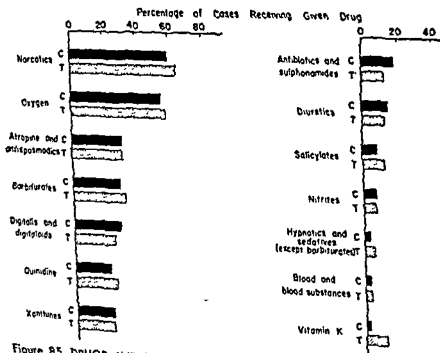


Figure 85. DRUGS AND THERAPEUTIC AGENTS RECEIVED: *Percentage of cases in control and treated groups receiving various types of drugs and therapeutic agents during the six-week period of observation.*

Fortunately for the study, the influence of this treatment difference on outcomes was probably small. Chapter VIII indicates that thromboembolic complications, the major focus of the present experiment, were apparently unrelated to type of hospital care. On the other hand, it is conceivable that a few deaths may have been prevented in the treated group by intensive nursing care. Since the excess of treated group cases receiving private duty nursing care amounted only to 19 cases,[e] and since such service was only one of many factors influencing mortality, deaths prevented by this excess of private duty nursing care probably did not exceed two or three at most.[f] The addition of three deaths would have increased the treated group percentage dying by less than one per cent. The influence of any imbalance in nursing service is thus inconsequential in the total picture.

Drug Therapy Other than with Anticoagulants

The drugs received by the patients constitute another important phase of patient management requiring examination. The reporting form included a request for a listing of all the drugs given to each patient during the period of observation and the dosage of each prescribed. These were broadly classified according to standardized procedures into a few major types. Tabulations reporting the findings for each type of drug of interest for this study appear in Table 88, Appendix F Table 35 and graphically in Figure 85. No attempt was made to analyze

[e] This excess was computed by applying the control group nursing rates for the various component subgroups to corresponding treated group base counts and subtracting the result from the actual number receiving such care.

[f] The estimate is a rough approximation only. Because of the selection by severity involved in determining which patients receive private duty nursing care, precise statistical estimates of savings based on the corresponding experience of those patients who did not receive such nursing care would not be valid.

TABLE 88

DRUGS RECEIVED: Percentage of Cases in the Total Sample and in the Control and Treated Groups Receiving Various Types of Drugs and *Therapeutic Agents other than Anticoagulants* during the Six-Week Period of Observation

Type of Drug[a]	Percentage of Cases Receiving Drug[b]		
	Total Sample	Control Group	Treated Group
Narcotics	63.1	60.2	65.4
Oxygen (by tent, mask or nasal catheter)	57.4	56.1	58.4
Hypnotics and sedatives:			
Barbiturates	31.0	29.4	32 3
Nonbarbiturates	4.8	3.4	5.8
Total hypnotics and sedatives	*32.9*[c]	*30.3*[c]	34 5[c]
Atropine and antispasmodics	31.7	31.4	31.9
Digitalis and digitaloids	27.2	29.0	25.8
Quinidine	24.5	22.6	26 0
Xanthines	23.8	23 5	23.9
Antibiotics and sulfonamides:			
Penicillin	14.2	17.2	11.9
Streptomycin	.8	.9	.7
Sulfonamides	2.1	2.7	1.7
Total antibiotics and sulfonamides	15.5[c]	18.8[c]	13.1[c]
Diuretics	14.3	15.6	13.2
Salicylates	10.9	8.8	12.4
Vitamin K	8.0	2.3	12 2
Nitrites	7.4	7.5	7.3
Blood and blood substances:			
Fresh whole blood	1.6	.7	2 2

[a] Counts exclude drugs of no interest to the study and drugs received by only one or two persons.

[b] Reports of drugs received are undoubtedly incomplete, particularly for the periods before hospitalization and after discharge.

[c] Total count is less than the sum of the components because cases receiving two more subtypes are counted only once.

[d] Probably underreported. Excludes mineral oil.

Miscellaneous Aspects of Management

The following details regarding other aspects of management warrant comment:

Bed Rest

Treatment in the form of absolute bed rest, while not specifically covered on the report forms was obviously conservative. The recommendations of Irvin and Burgess[89] favoring early ambulation after only two weeks of bed rest were published after the termination of this study. So also was the proposal of Levine and Lown[117] that patients be placed in a chair for 1 or 2 hours daily after the first day of the illness, as well as Littman's[123] favorable experience with increased activity in bed and early ambulation. There is thus every reason to believe that the more traditional policies of absolute quiet characterized the management of both groups.

Restricted Sodium Intake

Reports regarding the restriction or nonrestriction of sodium were received for 1016 patients. Of these, sodium was reported restricted in 41 per cent. The control and treated groups were fully comparable in this respect, the percentage thus restricted being the same for each treatment group (41 per cent). No analysis was attempted of the degree and duration of such restriction.

Fluid Limitation

While the schedule also asked whether fluids were limited, the replies on this point were not tabulated. It was clear from inspection, however, that fluids were only occasionally restricted in either group.

For a discussion of other aspects of management of myocardial infarction, the reader is referred to Wright.[224]

ADMINISTRATION OF ANTICOAGULANTS

The differences with respect to anticoagulant therapy present a sharp contrast to the similarities between treatment groups characteristic of other aspects of management. Since the present study endeavors to evaluate the assets and liabilities of anticoagulant therapy for coronary thrombosis with myocardial infarction, a statement of the procedures used in the application of this therapy to the treated group is necessary for the careful definition of the conditions of the clinical experiment. The methods of administering dicumarol recommended to the participating hospitals are reproduced on page 11. The actual doses used and the prothrombin levels maintained are described at length in Chapter XII. Experience with heparin in the present study is the subject of a special chapter (see Chapter X). Details are given in the present section regarding (1) the anticoagulant drugs used, (2) the proportion of the illness period protected with anticoagulants, and (3) changes in anticoagulant coverage by week of illness. Other miscellaneous details regarding the anticoagulants employed will follow at appropriate points.

Anticoagulants Used

Dicumarol was the anticoagulant most frequently used in the present study. Heparin, the only other anticoagulant administered, was given to only a small proportion of the patients. The relative extent to which dicumarol and heparin were used is shown in Table 89 and Figure 86. From Table 89 it can be computed that, of the 612 patients who received some type of anticoagulant therapy, 81.2 per cent received dicumarol only, 18.3 per cent received both dicumarol and heparin, and 3 patients (0.5 per cent) received heparin only. Heparin was more extensively used for patients in the control group than for those in the treated group because emergency thromboembolic conditions developed which required that exceptions be made.

The extent to which "treated group" cases were exempted from anticoagulant treatment and "control group" cases received anticoagulant therapy is also made

about a third of the cases (32 per cent). Thirty-one per cent received sedation in the form of barbiturates. Twenty-seven per cent received digitalis or the digitaloids, presumably for the control of congestive heart failure. Quinidine, prescribed in myocardial infarction because of its effect in reducing irregularities of rhythm was received by 25 per cent. Twenty-four per cent of the patients were given xanthines, probably because of the alleged ability of these drugs to dilate the coronary arteries, thus increasing the supply of oxygen to the myocardium. Concurrent infections, such as pneumonia and cystitis, were treated with antibiotics and sulfonamides in 16 per cent of the cases. Diuretics were used in 14 per cent of the patients, and 11 per cent of the patients received salicylates of some type.

All other drugs, with the exception of anticoagulants, were used with less than 10 per cent of the patients. Eight per cent received vitamin K to control hypoprothrombinemia. Seven per cent received nitrites, probably for their vasodilator effect. Five per cent received hypnotics and sedatives not in the barbiturate group. To combat shock or hemorrhage or both, 3.2 per cent were given blood or blood substitutes in some form. The sympathominetic drugs (adrenalin, ephedrine, etc.) were prescribed for 1.3 per cent; rutin, for 0.7 per cent; and coramine, for 0.5 per cent. Other details appear in Table 88 and Appendix F Table 35. Use of vitamins and cathartics was probably underreported, while some types, such as mineral oil and certain vitamins were not tabulated. Newer drug therapies, such as the use of nor-epinephrine for shock, were not in use at the time of this study.

Differences between treatment groups were usually small and were not statistically significant except in respect to (1) use of vitamin K and (2) use of penicillin. The difference in respect to vitamin K, a highly significant one statistically, was clearly a consequence of the use of anticoagulants, vitamin K being the first resource when excessive prolongation of prothrombin times occurred. Fresh blood was also used more frequently for the treated group, probably for the same reason, but the differences in this instance (0.7 per cent, control, *vs.* 2.2 per cent, treated) were not quite sufficient to be statistically significant as defined for this study. The difference in the case of penicillin was only of borderline significance. It seems likely, however, that its greater use in the control group was related, in part, to the larger number of pulmonary infarctions in this group and to the confusion of some pulmonary infarctions with pneumonia.

Other differences were of mixed direction (see Figure 85) and not statistically significant. The slightly greater use made of narcotics, oxygen, barbiturates, and salicylates in the treated as compared with the control group may possibly be related to the greater severity of these cases at onset (pages 64-65). The greater use of diuretics in the control group, on the other hand, may be related to the somewhat greater proportion of cases showing congestive heart failure in this group, the reasons for which were evaluated in Chapter VI.

Thus the drug analysis supports in general the conclusion that, except for anticoagulants and drugs related to their obvious consequences, the drug therapy received by the two groups was approximately comparable. This finding lends further support to previous deductions that the medical condition of the two groups at onset was approximately similar. There is further no reason to believe that any of the small differences for drugs other than anticoagulants could be responsible for the substantial differences in deaths and thromboembolic complications reported in subsequent chapters. Moreover, with the exception of drugs to counteract hypoprothrombinemia, the drug findings do not point to any ancillary effects from anticoagulants that required changes in other aspects of drug therapy.

of dicumarol is operating in a progressively less effective manner.

For these reasons, in calculating the number of days during which a case was under the influence of dicumarol, the days under anticoagulant therapy were enumerated in 3 subcategories as follows: (1) the first 3 days of anticoagulant therapy, (2) days between the 4th day of therapy and the last dose of dicumarol inclusive, and (3) the 4 days after the last dose of dicumarol. If dicumarol therapy is carried out in perfect accord with current practice, cases receive the maximum protection against thromboembolic complications during the period between the 4th day and the day of the last dose inclusive, but receive something less than complete protection during the periods of the first 3 days and following the last dose. Actually, protection is probably often less than that intended because of the failure in many instances to maintain the prothrombin activity within the therapeutic range of 11 to 23 per cent of normal (see page 362).

Counts of the number of patient-days of anticoagulant therapy reveal the extent to which the treated group actually received anticoagulants. These detailed counts are given in Appendix F, Table 36 along with those for the control group. Figure 87 shows graphically the proportion of the total observed days on which treated group cases received anticoagulants.

From these data it is evident that even among those cases treated with anticoagulants, protection by anticoagulant therapy

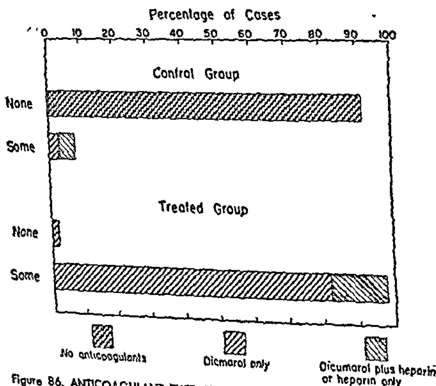


Figure 86. ANTICOAGULANT THERAPY GIVEN: Percentage of cases in control and treated groups never receiving anticoagulants during the six-week period of observation and corresponding percentages for cases receiving some anticoagulant therapy, the latter subdivided into percentage receiving dicumarol only and dicumarol plus heparin (or heparin only).

clear in Figure 86. The explanations for these anomalies are to be found in Chapter III.

Proportion of Illness Period Protected with Anticoagulants

In evaluating the findings of this study, it is important to recognize that treated group patients were not protected with anticoagulants the entire six-week period of observation. Only four weeks of anticoagulant therapy were originally recommended, or for cases developing complications, four weeks after the last thromboembolic development. Even this period of protection was shortened for some patients through delayed admission or early discharge from the hospital, death during the period of observation, deviations in the policies of individual hospitals or physicians, development of bleeding episodes, and temporary contraindications, such as unexpected operations.

The period of *effective anticoagulant therapy* was further shortened by the usual delay in the patient's response to dicumarol. When dicumarol therapy is initiated in the usual manner (i.e., when a dose of 200 or 300 mg. is given on the first day and doses on the following days are determined by the prothrombin time on each given day), approximately 3 days of such therapy is ordinarily required before the prothrombin time is prolonged to the degree commonly accepted as producing adequate anticoagulant action. Materially larger doses of dicumarol may shorten this period moderately and smaller doses may postpone indefinitely the attainment of an adequate prothrombin level, but within the dosage limits generally used in this study, an average of 3 days is required. During this period of time, then, dicumarol therapy alone produces something less than ideal anticoagulant effect.[a] For a more detailed discussion of this problem see Chapter XII.

Similarly, when dicumarol therapy is discontinued, the prothrombin activity of the plasma does not return promptly to normal, but requires a period of from 2 to 7 days (averaging about 4 days) to do so. During this period of time the anticoagulant action

[a] Tromexan produces a more rapid response (see article evaluating this drug reproduced as Appendix A of this report).

TABLE 89

TYPE OF ANTICOAGULANT GIVEN: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Receiving Dicumarol and/or Heparin during the Six-Week Period of Observation

Type of Anticoagulant Therapy Given	Number of Cases			Percentage of Cases		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
Some anticoagulant therapy:						
Dicumarol only	497	13	484	48.2	2.9	82.2
Dicumarol plus some heparin	112	21	91	10.9	4.8	15.5
Heparin only	3	1	2	.3	.2	.3
Total receiving some anticoagulant therapy	612	35	577	59.4	7.9	98.0
No anticoagulant therapy[a]	419	407	12	40.6	92.1	2.0
Total cases	1031	442	589	100.0	100.0	100.0

[a] Six cases received so little anticoagulant therapy that they were tabulated throughout the study in the "no anticoagulant" category of the control group (see footnotes b and c of Table 3).

of dicumarol is operating in a progressively less effective manner.

For these reasons, in calculating the number of days during which a case was under the influence of dicumarol, the days under anticoagulant therapy were enumerated in 3 subcategories as follows: (1) the first 3 days of anticoagulant therapy, (2) days between the 4th day of therapy and the last dose of dicumarol inclusive, and (3) the 4 days after the last dose of dicumarol. If dicumarol therapy is carried out in perfect accord with current practice, cases receive the maximum protection against thromboembolic complications during the period between the 4th day and the day of the last dose inclusive, but receive something less than complete protection during the periods of the first 3 days and following the last dose. Actually, protection is probably often less than that intended because of the failure in many instances to maintain the prothrombin activity within the therapeutic range of 11 to 23 per cent of normal (see page 362).

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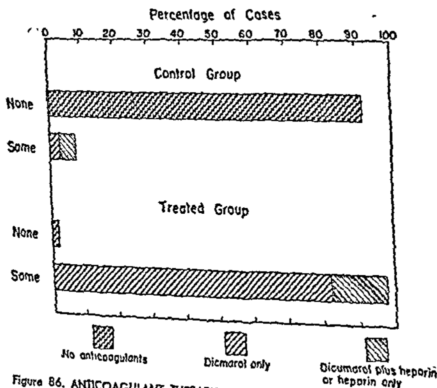


Figure 86. ANTICOAGULANT THERAPY GIVEN: *Percentage of cases in control and treated groups never receiving anticoagulants during the six-week period of observation and corresponding percentages for cases receiving some anticoagulant therapy, the latter subdivided into percentage receiving dicumarol only and dicumarol plus heparin (or heparin only).*

was far from complete or ideal. Of the total of 21,854 days of observation for the treated group, 26 per cent were days when the patients were not under anticoagulants, 8 per cent were days during the first 3 days of anticoagulant therapy, 59 per cent were days between the 4th day of such therapy and the day of the last dose inclusive, and 7 per cent were days after termination but within 4 days of the last dose. Thus, while 74 per cent of the days observed for the treated group were in one sense under anticoagulants, adequate protection from thromboembolic complications could at best have been *expected only* for the period from the 4th day of such therapy through the day of the last dose, or in this study, for less than two-thirds of the total time observed for the treated group. Even within this portion of total time, doses were commonly inadequate to maintain patients within recommended range, as Chapter XII demonstrates. Under these circumstances, the reduction in the rate of thromboembolic complications characteristic of the treated group (described in Chapter VIII) cannot be said to represent the maximum gain possible with anticoagulant therapy.

Changes in Proportion Receiving Anticoagulant Therapy by Week of Illness

Figure 87 and Appendix F Table 36 can also be used to ascertain fluctuations in coverage with anticoagulants by week of illness. A high proportion of the time during the first week was necessarily devoted to the initial stages of therapy. As would be expected, more than half of the days of anticoagulant therapy administered in this week fell within 3 days of the first dose. The com-

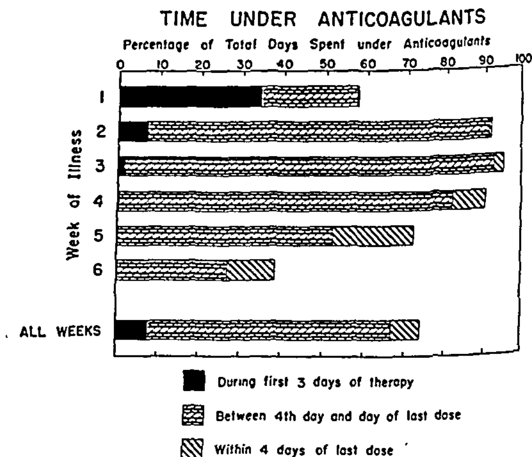


Figure 87. TIME UNDER ANTICOAGULANTS: Percentage of total days observed for treated group during which patients were in various stages of anticoagulant therapy, by week of illness.

onent representing initial therapy diminhed rapidly into insignificance thereafter. ime after, but within 4 days of, the terminal lose became an important component of otal therapy time only from the 4th week on. It was highest in the 5th week when it constituted 20 per cent of the total days. Potentially effective therapy (i.e., that between the 4th day and the day of the last dose) was at its maximum during the 3rd week when 92 per cent of total days observed were for the 4th day or later of therapy. The 2nd and the 4th weeks also showed that on over 80 per cent of the days the patients were beyond the initial stages of therapy.

Anticoagulants were not in effect at all for more than two-fifths of the time during the first week, due to delays in hospitalization, delays in beginning therapy, and contraindications The unfortunate consequences of these delays are apparent in the relatively high rate of thromboembolic complications in the treated group before the beginning of therapy, namely, 9.7 per thousand such days observed (see Table 95, Chapter VIII) After the first week, days covered by anticoagulants remained above 90 per cent of total days for the 2nd, 3rd, and 4th weeks, but dropped off rapidly thereafter as anticoagulants were discontinued and patients discharged. The risk incurred through termination at this stage appears to have been minimal as contrasted with that shortly after the attack, for the rate of complications after tw

da

or

tu ...rapy even though more than 3,000 days of illness were observed following termination

The foregoing comments relate only to the treated group. Because the control group received very little anticoagulant therapy (actually less than 5 per cent of total days observed), and because this therapy occurred under exceptional circumstances and was usually delayed, data of a corresponding type for the control group have no significance as a picture of the typical pattern for dicumarol therapy and are not shown graphically.

SUMMARY

This chapter has been concerned with the nature of the treatment received by the control and treated groups. The average time prior to hospital admission was found to be 2.5 days and the time prior to diagnosis, 2.7 days. Forty-four per cent of the patients were admitted on the first day of their illness while 6 per cent were admitted only after the eighth day. Patients were hospitalized for 29 days on the average, excluding time after the termination of the period of observation. About a third were private or semiprivate patients and 10 per cent received some service from a private duty nurse. The drugs most commonly used, other than anticoagulants, when stated in descending order of the proportion receiving them, were: narcotics,

...other types of drugs except anticoagulants were used for less than 10 per cent of the cases. Sodium was restricted for 41 per cent.

No evidence of lack of comparability in treatment in respects other than anticoagulant therapy was found that was not readily explainable either on a chance basis or in terms of an indirect relation to anticoagulant therapy with one exception, namely a difference of borderline significance for private duty nursing. While the fact that the treated group was about 5 percentile points above the control group was perhaps not due to chance, the effect of this difference on the outcomes used to evaluate anticoagulant therapy was considered to be minor or inconsequential. All other differences that reached statistical significance or borderline status, as determined by the standards for significance levels adopted for this study, were: the use of vitamin K, the average days

spent in the hospital, and the proportion of cases receiving penicillin. All three were presumably related to anticoagulant therapy. Vitamin K was used to a greater extent for the treated than for the control group because of the occasional need to counteract the hypoprothrombinemia effect of anticoagulants. The slightly longer hospitalization received by the treated group clearly resulted in the main from the higher death rate in the control group. The greater use of penicillin in the control group may be related to the greater frequency of pulmonary infarctions which was observed among patients in this group.

With these few exceptions, the analysis revealed no differences in the treatment received by the two groups that exceeded reasonable chance limits, that reflected any differences in the needs of the two groups, that suggested any adverse effects of anticoagulant therapy itself (other than hemorrhagic complications), or appeared capable itself of producing any important differences in outcomes. The differences in outcomes in respect to deaths and thromboembolic complications cannot therefore be explained in terms of any difference in the treatment received by the two groups other than that in anticoagulant therapy which the study was designed to evaluate.

Anticoagulant therapy was begun for the treated group on the average early on the fourth day after onset. Dicumarol was the principal anticoagulant used. Treatment during the early period was supplemented with heparin in only about a fifth of the cases. Protection was typically suboptimal during the first week and was usually discontinued before the sixth week. Altogether about 59 per cent of the total period of observation for the treated group came within the period of potentially effective anticoagulant therapy with dicumarol, namely, the period between the fourth day of anticoagulants and the day of the last dose. Even within this period of potential protection, doses were commonly inadequate to maintain patients within the optimum therapeutic range. *Thus the outcomes reported in later chapters cannot be said to represent the maximum gain possible with anticoagulant therapy*

CHAPTER VIII

Thromboembolic Complications

HAT thromboembolic phenomena are mmon complications of coronary occlusion h myocardial infarction and that they itribute significantly to the morbidity and rtality among patients who have recently fered a myocardial infarction are observans which have been made repeatedly rough the years. Less widely appreciated the medical profession is the fact, emphaed for a decade or more in papers by rious authors, that these complications cur far more often than is recognized clinally. This fact has been again confirmed in e present study, as Chapter XIII dealing ith the autopsy findings will demonstrate.

The value of anticoagulant therapy in ronary thrombosis with myocardial inrction lies primarily in its power to reduce ie incidence of these thromboembolic comlications during the four-week period of xceptionally high risk of such complications llowing the attack of coronary thrombosis. review of the success of this therapy in chieving this aim in the present study is he purpose of this chapter. The presentations limited to a discussion of the clinical findngs. Supplementary evidence of the effeciveness of anticoagulants in this regard ppears in Chapter XIII which deals with he autopsy findings.

The first part of the present chapter deals with the over-all evidence regarding the reluction in thromboembolic complications achieved with anticoagulants. The second part of the chapter presents data on the types of patients that are most prone to develop complications and the relative effectiveness of anticoagulants in protecting these various types. The major topics considered are as follows:

A. Definition of term "thromboembolic complications" as used in this chapter.

B. Major findings for all patients in the control and treated groups with respect to:
   1. Proportion of patients developing complications
   2. Average number of thromboembolic complications developed
   3. Extent of single and multiple episodes
   4. Complication rates at various stages of therapy compared with control group rates for comparable periods of time
   5. Types of complications developed
   6. Incidence of complications by week of illness
   7. Incidence of complications by prothrombin levels

C. Incidence of complications and variations in the effectiveness of anticoagulants in relation to the following characteristics of patients:
   1. Age
   2. Sex
   3. Severity of attack
   4. Weight
   5. Economic level (i.e., ward *vs.* private patients)
   6. Site of original infarction
   7. Abnormal rhythms
   8. Shock and congestive heart failure

DEFINITIONS

Types of Thromboembolic Phenomena Included

To be included in the counts of thromboembolic complications reported in this chap-

ter, a complication must have been diagnosed clinically, must have been considered definite or probable on the basis of clinical evidence, and must have occurred within the six-week period which followed the onset of the initial acute attack of coronary occlusion with myocardial infarction. Thromboembolic complications recognized for the first time at autopsy are excluded from the tables in this chapter, but are tabulated and discussed in the chapter concerned with autopsy findings.

Counts of thromboembolic complications include both those which occurred in vessels outside of the heart ("extracardiac") and those which involved the coronary circulation ("intracardiac"). The former have been tabulated and are discussed in four subcategories: (a) pulmonary emboli, (b) cerebral emboli, (c) peripheral and visceral emboli, and (d) venous thromboses. The "intracardiac" complications are divided into two groups according to their location: (a) extensions of the original myocardial infarction and (b) new areas of myocardial infarction. Classifications were again based on clinical diagnoses. The extent of agreement with autopsy findings is discussed in Chapter XIII. Further discussion of each of these categories appears on pages 210–217.

Handling of Doubtful Diagnoses

As discussed in a previous section of this report, the participating hospitals were asked to support each diagnosis of a thromboembolic complication occurring in patients during the six-week period of observation with a clinical description of the episode. When doubt was expressed by the attending physician, a statement of the evidence upon which the diagnosis was based was requested. As case reports were reviewed in the Central Laboratory, the certainty of each diagnosis was classified as "definite," "probable," or "improbable" according to the reported evidence and the assurance expressed by the physician in attendance. In doubtful cases, correspondence with the hospital of origin usually served to obtain a review of the evidence on which the diagnosis was based and to clarify the status of the individual case in this respect. In a few instances there was disagreement between the final opinion of the reviewer and the reporting hospital, but in such instances, the opinion of the physician who had attended the case was accepted as final for purposes of classification.

On this basis, 218 of the 268 episodes suggesting thromboembolic complications mentioned in reports for the total series were considered "definite" complications, 31 were classified as "probable" complications and 19 were felt to be "improbable." The 249 thromboembolic complications classified as "definite" or "probable" are used in all subsequent tabulations of complications, while the 19 episodes which were classified as "improbable" have been dropped from further consideration.

As shown in Table 90, 154 of the thromboembolic complications reported for cases in the control group were "definite," and 18 were "probable." Thirteen suspected episodes (7 per cent of the total) were adjudged "improbable" and were discarded from the analysis. For the treated group, 64 complications were "definite" and 13 were considered "probable." Six possible episodes (also 7 per cent of the total) were felt to be "improbable" and were discarded from the analysis. Since the proportion eliminated in the two groups was the same, differences between the control and treated groups cannot be explained on this basis.

Uncertainty with respect to the exact diagnosis was most frequent in the case of cerebral and pulmonary emboli. Fourteen of the 19 improbable diagnoses fell in these two categories. Cerebral episodes constituted a diagnostic problem because of the difficulty of distinguishing cerebral emboli from cerebral hemorrhages and temporary functional disturbances. In the case of suspicious pulmonary symptoms the problem was primar-

ily that of distinguishing embolic phenomena om pneumonia.

About two-thirds (64 per cent) of the "extensions" of the original myocardial infarcions reported as definite or probable were upported by an electrocardiographic diagnosis of further myocardial damage; the others were reported as extensions only by the statement of the attending physician. Since the original reporting forms did not provide for the systematic reporting of evidence, actual electrocardiographic evidence of extensions may have been more universal than these figures indicate. In contrast, about nine-tenths (86 per cent) of the new infarctions considered definite or probable were supported by an electrocardiographic diagnosis. In the remaining instances, the certainty of diagnosis rests solely on the attending physician's evaluation of the clinical picture. This evaluation presumably was based on essentially the same clinical criteria for the diagnosis of coronary thrombosis with myocardial infarction as were recommended at the onset of the study.

BASIC FINDINGS FOR TOTAL GROUP

Cases Developing One or More Thromboembolic Complications

General Findings

After a decision had been reached as to whether each reported episode was, or was not, a thromboembolic complication according to the foregoing definitions, numerous actual counts were made, the first of which related to cases developing complications. The actual thromboembolic record achieved through anticoagulant therapy is strikingly evident in Table 91 and Figure 88 which compare the control and treated groups in this respect.

TABLE 90

COMPLICATIONS INCLUDED AND EXCLUDED: Number and Percentage of Reported Episodes Suggesting Thromboembolic Complications Considered *after* Review to Have Been Definite or Probable Complications (Included in Counts) and Number and Percentage Considered Improbable (Excluded from Counts), by Treatment Groups

Complications Included and Excluded	Thromboembolic Complications					
	Number Reported*			Percentage of Total		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
Complications included in counts.						
Episodes diagnosed as:						
Definite complications	218	154	64	81	83	77
Probable complications	31	18	13	12	10	16
Total complications included in counts	249	172	77	93	93	93
Complications excluded from counts (complication considered improbable by reporting hospital)	19	13	6	7	7	7
Total episodes suggesting thromboembolic complications reviewed.	268	185	83	100	100	100

* In all other tab[illegible]

One hundred and fifteen, or 26.0 per cent of the 442 cases in the control group, developed one or more thromboembolic complications during the six-week period of observation following the initial coronary occlusion with myocardial infarction. No patient in this group was receiving anticoagulant therapy at the time the first complication occurred; hence no corrections for exceptions in treatment are necessary in this figure. In contrast to the control group, 64 patients, or only 10.9 per cent of the treated group, developed one or more thromboembolic complications during the corresponding period.[a] *Thus even though the treated group received anticoagulants for only part of the six-week period and sometimes in inadequate amounts, less than half as many persons per 100 developed thromboembolic complications as in the corresponding control group. The difference is highly significant statistically.*[b] *Since it cannot be reasonably accounted for either by chance or by any of the various known but very minor differences between the two groups, it must be attributed directly to anticoagulant therapy.*

Time of First Complication

For purposes of further analysis, the treated group cases were subdivided into three groups according to whether their first thromboembolic complication occurred: (1) when the patient was not under anticoagulant therapy, (2) during the first three days of anticoagulant therapy, or (3) after the third day of anticoagulant therapy. These categories appear repeatedly throughout this and other chapters and have a uniform meaning.

[a] For equivalent rates that would have resulted if other definitions of the control and treated groups had been used, see Appendix F, Table 2.

[b] Observed difference was 15.1. The approximate 95 per cent confidence limits for the true difference between treatment groups were 10.2 and 20.0 per cent. The "95 per cent" designation means that these limits have been computed by a method that 95 out of 100 times it is used will correctly enclose the true difference between the populations randomly represented by the samples.

The period when the patient was not under anticoagulant therapy included: (a) the period prior to the administration of anticoagulants, including time on the first day of such therapy before the first dose was given, (b) the period following the termination of anticoagulants after the prothrombin time had returned to normal, (c) periods during the interruption of anticoagulant therapy when the prothrombin time was within normal limits, (d) the total period of observation for patients not receiving anticoagulants at any time.

The period after the third day of anticoagulant therapy included all thromboembolic complications occurring from the

TABLE 91

CASES DEVELOPING COMPLICATIONS: Percentage of Cases in the Control and Treated Groups Developing One or More Thromboembolic Complications and Status of Anticoagulant Therapy at Time of First Complication

Status of Anticoagulant Therapy at Time of First Complication	Percentage of Cases Developing One or More Thromboembolic Complications[a]	
	Control Group (442 Cases)	Treated Group (589 Cases)
First complication occurring while patient not under anticoagulants.......	26.0	3.6
First complication occurring during first three days of anticoagulant therapy...	—[b]	1.2
First complication occurring after third day of anticoagulant therapy.......	—[b]	6.1
All cases . . .	26.0	10.9

[a] For actual counts, see Appendix F Table 41.

[b] There are no cases in these categories since all control group cases for whom exceptions were made (35 cases) received anticoagulants only *after* one or more complications had developed. The 31 cases admitted on even days who received anticoagulants preventively for miscellaneous reasons at least two days before a thromboembolic complication developed or who developed no complication at all were analyzed as part of the treated group (see p. 20).

fourth day of anticoagulant therapy through the day of the last dose and thereafter until the prothrombin time had returned to 17 seconds or less, converted (or to 58 per cent or more of prothrombin activity). When no data were given on prothrombin times sub-equent to the day of the last dose, as very requently happened, times were estimated o be normal beginning with the fifth day fter the last dose of dicumarol.

When the 64 cases in the treated group leveloping complications were considered in his manner, it was found that 21, or about a third of those developing complications, developed their first complication when they were receiving no anticoagulants, usually before the initiation of therapy. Another 7 patients developed their first complication during the first three days of anticoagulant therapy. Since none of these was receiving heparin when the complication developed and dicumarol cannot be expected to be fully effective during this initial stage, these complications cannot be considered a failure of such therapy although they reveal one of its shortcomings.

The remaining 36 patients, or slightly more than half of those developing complications, developed their first complication after the third day of anticoagulant therapy. This does not necessarily indicate that these complications occurred in patients under the full influence of such therapy, for in some instances the degree by which the prothrombin time was prolonged at the time of such a complication was less than that which would ordinarily be considered adequate anticoagulant therapy.

Percentages for these component periods are not directly comparable with the control group figure of 26.0 per cent since the control group case rate applies to the total six-week period and must be compared only with the total six-week rate for the treated group, namely, with 10.9 per cent. A technique for

CASES DEVELOPING COMPLICATIONS

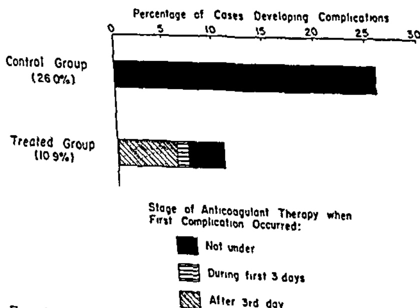


Figure 88. CASES DEVELOPING COMPLICATIONS: Percentage of cases in control and treated groups developing one or more thromboembolic complications and status of anticoagulant therapy at time of first complication.

comparing subperiods is presented in a later section (pages 206–210).

Number of Thromboembolic Complications Developed

General Findings

Since many patients developed more than *one thromboembolic complication, the total* number of complications diagnosed in the series exceeds substantially the number of cases for whom complications were diagnosed. The 115 patients in the control group who developed complications suffered, for example, a total of 172 "definite" or "probable" thromboembolic complications during the six-week period of observation following the initial coronary occlusion with myocardial infarction. In contrast, the 64 patients in the treated group who developed at least one complication suffered a total of only 77 "definite" or "probable" thromboembolic complications during the same period.

When these counts are expressed in terms of the average number of thromboembolic complications per 100 cases, the figures become 38.9 thromboembolic complications per 100 cases in the control group and only 13.1 thromboembolic complications per 100 cases in the treated group. The difference is highly significant statistically.[*] *Again the effect of anticoagulants is strikingly apparent.*

These figures are based on the findings as reported. The difference between the two groups is increased when a conservative correction is made for the occasional use of anticoagulants for the 35 control group patients who received anticoagulants as an exception, as previously explained (see Chapter III), *after the development of one or more thromboembolic complications.* By assuming that if these 35 patients had not received anticoagulants at any time they would have developed complications during the period of anticoagulant therapy at the same rate as did similar control group patients at similar stages of their illness who did not receive the aid of anticoagulants, it was possible to estimate the approximate savings effected by the use of anticoagulants with these 35 control group patients. The estimates thus arrived at indicated that without any anticoagulants whatsoever the control group would have developed an additional 12.9 complications, or a total of 184.9 complications (an average of 41.8 complications per 100 patients). Table 92 and Figure 89, which illustrate these findings, both include this correction. The estimate added is conservative since no group could be found to use as the basis for estimates that was in as serious condition with respect to complications as

[*] When tests of significance are reported in the present chapter, it should be assumed that the tests were applied to differences before corrections for exceptions in treatment (see explanation in Appendix C). In order not to confuse the reader, the text usually omits reference to this standard qualification applicable routinely to all such tests.

TABLE 92

NUMBER OF COMPLICATIONS: Average Number of Thromboembolic Complications per Hundred Cases in the Control and Treated Groups and Status of Anticoagulant Therapy at Time *Complication Developed*

Status of Anticoagulant Therapy at Time Complication Developed	Average Number of Thromboembolic Complications per 100 Cases[a]	
	Control Group[b] (442 Cases)	Treated Group (589 Cases)
Complications occurring while patient not under anticoagulants	41.8	4 6
Complications occurring during first three days of anticoagulant therapy	—	1.7
Complications occurring after *third day of anticoagulant* therapy	—	6 8
All complications	41.8	13 1

[a] For actual counts, see Appendix F. Table 42.

[b] Data are corrected for exceptions in treatment. For this reason no complications under therapy are shown in the control group even though some control cases received anticoagulants as an exception.

was the group for whom exceptions actually were made. The details of the procedure by which the estimate was arrived at are explained in Appendix B.

To avoid confusing the reader with both corrected and uncorrected figures, the text, tables and figures throughout this chapter hereafter will report only control group counts corrected for exceptions in treatment. However, Appendix F tables or footnotes almost always report the full details including figures and rates both before and after corrections for exceptions. It is therefore possible for any interested reader to ascertain in each instance what effect this estimating procedure had on the findings. *For technical statistical reasons and for purposes of conservatism, statements of statistical significance, even though mentioned in a context of corrected figures, were computed always from uncorrected rates which show a lesser difference in any comparison between the control and treated groups. These tests therefore indicate what the chances are that the lower uncorrected figure would occur on a chance basis.*

Time of Occurrence

Of the 77 thromboembolic complications suffered by the treated group, 27 (4.6 per 100) occurred when the patients were not under the influence of anticoagulants and 10 (1.7 per 100) occurred during the first three days and at times when patients were not receiving supplemental protection with heparin. Only 40 complications (6.8 per 100) occurred after the third day of anticoagulant therapy. Even with respect to these, one must reiterate that not all cases under anticoagulant therapy were receiving fully adequate therapy at all times. In Chapter XII it is estimated that with adequate therapy, the rate during the last of these periods might have been reduced by about one-third.

NUMBER OF COMPLICATIONS

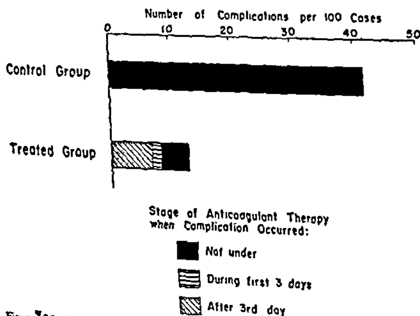


Figure 89. NUMBER OF COMPLICATIONS: Average number of thromboembolic complications per hundred cases in the control and treated groups and status of anticoagulant therapy at the time complication developed.

TABLE 93

CASES DEVELOPING COMPLICATIONS IN THIS SERIES AND NINETEEN OTHER SERIES OF MYOCARDIAL INFARCTION: Percentage of Cases Developing One or More Thromboembolic Complications in This Series and in Nineteen Other Series Reported in the Literature in Which Anticoagulants Were Used in the Treatment of Coronary Occlusion with Myocardial Infarction and for Which a Control Group Was Provided

Author(s)	*Number of Cases Observed*[a]		Percentage of Cases Developing One or More Thromboembolic Complications	
	Control Group	Treated Group	Control Group	Treated Group
1. This series	442	589	26.0	10.9
2. Beckwith & Gage[41]—Chesapeake & Ohio, Clifton Forge, Virginia	100	108	14.0	1.9
3. Bresnick *et al.*[77]—Boston City	128	122	20.3	15.6
4. Carmichael & Oetting[44]—U.S. Naval Hospital, Long Beach	43	30	27.9	6.7
5. Feldman *et al.*[61]—Cook County, Chicago	76[b]	76[b]	8.0[b]	5.3[b]
6. Furman *et al.*[a]—Vanderbilt University Hospital, Nashville	240[c]	74[c]	11.0[d]	5.0[d]
7. Greisman & Marcus[74]—Lincoln, New York	100	75	21.0	10.7[e]
8. Hilton *et al.*[81]—Montreal General	38	38	31.6	18.4
9. Holten[91, 92]—Municipal Hospital, Aarhus, Denmark	256	174	14.1	4.0
10. Loudon, Pease & Cooke[111f]—Radcliffe Infirmary, Oxford	125	75	21.6[f]	14.7[f]
11. Manchester & Rabkin[111h]—Gallinger Municipal, Washington, D.C.	150	150	17.3	6.0
12. Parker & Barker[177]—Mayo, Rochester	100	100	37.0	8.0[i]
13. Peters, Doenges & Brambel[112]—Mercy, Baltimore	86	110	15.1[i]	2.7[j]
14. Rashkoff *et al.*[197]—Mount Sinai, New York	145	142	21.4	13.4
15. Richter, Del Nunzio & Swiller[211]—Coney Island, Brooklyn	150	150	20.0	10.0
16. Schilling[212]—St. Luke's, New York	60	60	20.0[k]	5.0
17. Smith, Keyes & Denham[214]—Henry Ford, Detroit	731[l]	189[l]	19.4[l]	12.2[l, m]
18. Tulloch & Gilchrist[221]—Royal Infirmary, Edinburgh	84	70	28.6	12.9
19. Vander Veer, Marshall & Kuo[231]—Pennsylvania, Philadelphia	51[l]	35[l]	23.5[l]	17.1[l]
20. Zeluff & Field[234]—Bellevue, New York	100[n]	80[n]	20.0[n]	5.0[n]
All other series (excluding cases in the present series)	2694	1761	18.9	8.6
All series	3136[o]	2350[o]	19.9[o]	9.2[o]

[a] Reports for series 1, 3, 4, 7, 8, 9, 12, 14, 15, and 18 exclude from the analysis cases dying within a short period after the attack or after admission to the hospital. The definition of the excluded period varies from study to study from 6 to 72 hours.

[b] Cases dying within 48 hours are included in these figures as the authors did not indicate that complications in such cases were excluded from their counts.

[c] Number of cases observed differs from that in Table 124, Chapter XI, since the above quoted complication rates were based on a mimeographed report appearing prior to publication.[74] The published report[44] included additional cases but complication rates were not given. Subsequent to the

Thromboembolic Complications, by Hospital

These findings have been based on the pooled experience of 16 hospitals.[4] They can also be considered as 16 separate experiments and the reports of each separately analyzed. Appendix F, Table 37 indicates what the results would have been if this procedure had been used but percentages are not cited because some of the hospital samples were very small.

The experience with complications in 15 of the 16 hospitals was favorable to anticoagulants regardless of whether case counts or counts of complications are used as the measures. The only unfavorable experience was in San Francisco Hospital, a hospital that contributed a very small number of cases (7 control cases and 18 treated cases). All hospitals showing rates favorable to anticoagulants showed differences in rates that were moderate or large. Significance tests for individual hospitals were not undertaken since a sequence of 15 out of 16 differences favorable to anticoagulants on 16 separate independent tests, assuming comparable treatment groups, would occur by chance less than once in 100 times even disregarding the amount of the difference. *The results thus demonstrate a favorable association between anticoagulant therapy and low complication rates regardless of whether the findings are analyzed as 16 separate experiments or as a single experiment.*

[4] For justification for pooling, see footnote h, p 309.

Thromboembolic Complication Rates in Other Studies

This favorable record with respect to thromboembolic complications in the present study has been repeated in numerous other studies as Table 93 indicates. This table summarizes a total of 19 studies which have presented usable counts on the number of myocardial infarction cases developing thromboembolic complications in control and treated groups. The basic list of studies reviewed in its preparation was the same as that covered by Table 124, Chapter XI, dealing with the fatality rates observed in other studies. (This list included 21 studies

above tabulation and that in Table 124, Chapter XI, a later published report by these authors[u] was received, giving a different number of observations and different complication rates. The trend, however, was the same as in the above figures.

[d] The original report leaves some doubt as to whether these figures represent number of complications or cases with complications.

[e] The original article quotes complication rates for the treated group based on complications occurring after dicumarol therapy was instituted. However, in conformity with procedures used elsewhere in this table, the above rate includes 5 cases developing complications prior to receiving dicumarol, as described by the authors.

[f] Tromexan was administered to some of the patients in this study.

[g] The original report leaves some doubt as to whether these figures represent number of complications or cases with complications. Myocardial infarctions were excluded and "adequate records of suspicious incidents were sometimes lacking."

[h] Some of the patients in this study were treated at home.

[i] Includes 3 cases developing co[illegible]

[j] Includes "clinical embolism" [illegible]

[k] Figure differs from that prev[illegible] complications clinically have been [illegible]

[l] Data include cases from this [illegible]

[m] Includes 8 cases with thro[illegible] ...oagulant therapy.

[n] Cases dying within 48 hours are included in these figures as specified by the authors.

[o] Corrected for duplicate reporting of cases in the present (American Heart) series included in series 17 and 19

other than the present one but since two did not report usable complication rates they do not appear in Table 93.) The list examined included all studies of anticoagulant therapy *specifically* in myocardial infarction which had been published and had come to the attention of the authors prior to September 15, 1953* and which met the four following requirements: (1) data in usable form were given for both control and treated groups at the same hospital (or at equivalent hospitals), (2) treatment (with minor exceptions) was not reported to have been allocated selectively on the basis of the judgment of the individual practitioner, (3) the anticoagulants used were dicumarol and/or heparin and, (4) corrections for overlapping, if any, with the same cases used for the present series could be made. The percentages cited do not agree in all instances with those published since, in order to secure maximum comparability, published information had to be supplemented in some instances with additional unpublished data from the authors. The listing is purposefully inclusive rather than selective and includes some studies in which the comparability of the treatment groups is open to some question. Further comments on sources of variation between studies appear on pages 310–311.

In order that the percentages quoted in Table 93 might refer to comparable periods of observation for the control and treated groups, complications in treated cases before the beginning, and after the termination of anticoagulant therapy have been included. Studies that have compared treated group rates for the period of actual therapy with control group rates for longer periods have been omitted unless corrections could be made for the time difference since otherwise the benefits of therapy are overstated. When the original data permitted, complications diagnosed only at autopsy have also been omitted. Since this distinction was not always clearly maintained by the authors quoted, some complications diagnosed only at autopsy may appear in the figures.

Inspection of Table 93 indicates that the findings of all these other studies consistently confirm the effectiveness of anticoagulants in reducing complications. *Among all 20 studies, not a single one showed comparative rates unfavorable to anticoagulants. Such consistency is exceedingly rare on a chance basis and is statistically highly significant.*

In addition to being consistent in direction, most studies showed contrasts in favor of anticoagulants that were substantial. When all the studies were pooled, the overall proportion of control group cases developing complications was 19.9 per cent and that for treated group cases, 9.2 per cent. If the present series is omitted, the figures become 18.9 per cent for control group cases and 8.6 per cent for treated group cases. These latter figures are shown graphically in Figure 90. *Thus the 19 other studies amply confirm the present study with respect to the generally lower proportion of cases developing complications under anticoagulant therapy.*

It is interesting to note in addition that the pooled levels for other studies are lower in both treatment groups than in the present study and that the contrast by treatment groups is slightly less. This generally lower level of complications in other studies could mean either that the cases included in the present series were more serious than the average or that the reporting of thromboembolic phenomena was more complete. The fact that the control group death rate is lower in the present series than in the others in this table† refutes the first of these expla-

* Kerwin,[106] in a study published subsequent to this tabulation, reports a reduction in complication rates under anticoagulants that is similar in amount to the reduction achieved in this study.

† The control group death rate for the other series in Table 93 after pooling and exclusion of all cases also in the present series and cases dying within 48 hours of hospitalization (i.e., in series where mortality rates including these cases were

nations and thus indirectly supports the second. Such a difference is also to be expected since considerable attention was given as the study progressed to encouraging the careful observation and recording of thromboembolic phenomena. In addition, some studies[70, 125] are known to have omitted intracardiac complications, a procedure that would also reduce the levels observed, while others used control groups from prior periods when there was less awareness of thromboembolic phenomena.[18, 70, 177, 218] *Thus the lower rates in other studies should not be taken as evidence that the findings of the present study are atypical.*

Five of the 19 studies reported, in addition, the number of thromboembolic episodes their patients experienced. When these counts were restated in terms of the average number of thromboembolic episodes per 100 cases, the results were as follows:

Authors	Control Group	Treated Group
Beckwith and Gage[18]	16.0	1.9
Bresnick *et al.*[25]	25.0	21.3
Carmichael and Oetting[49]	37.2	6.7
Rashkoff *et al.*[157]	26.2	14.1
Richter, Del Nunzio and Swiller[161]	22.7	10 0

also given—see Table 124, Chapter XI) was 29.8 per cent as compared with 23.4 per cent in the present series.

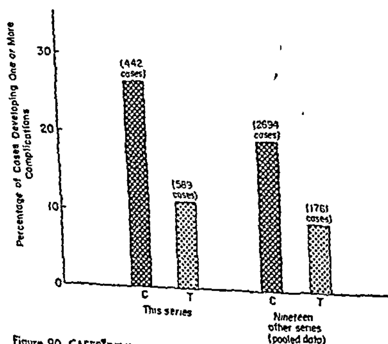


Figure 90. CASES DEVELOPING COMPLICATIONS IN THIS SERIES AND NINETEEN OTHER SERIES OF MYOCARDIAL INFARCTION: *Percentage of cases developing one or more thromboembolic complications in the control and treated groups in this series and nineteen other series (pooled) of myocardial infarction reported in the literature in which anticoagulants were used in the treatment of coronary occlusion with myocardial infarction and for which a control group was provided.*

other than the present one but since two did not report usable complication rates they do not appear in Table 93.) The list examined included all studies of anticoagulant therapy specifically in myocardial infarction which had been published and had come to the attention of the authors prior to September 15, 1953* and which met the four following requirements: (1) data in usable form were given for both control and treated groups at the same hospital (or at equivalent hospitals), (2) treatment (with minor exceptions) was not reported to have been allocated selectively on the basis of the judgment of the individual practitioner, (3) the anticoagulants used were dicumarol and/or heparin and, (4) corrections for overlapping, if any, with the same cases used for the present series could be made. The percentages cited do not agree in all instances with those published since, in order to secure maximum comparability, published information had to be supplemented in some instances with additional unpublished data from the authors. The listing is purposefully inclusive rather than selective and includes some studies in which the comparability of the treatment groups is open to some question. Further comments on sources of variation between studies appear on pages 310-311.

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* Kerwin,[106] in a study published subsequent to this tabulation, reports a reduction in complication rates under anticoagulants that is similar in amount to the reduction achieved in this study.

[f] The control group death rate for the other series in Table 93 after pooling and exclusion of all cases also in the present series and cases dying within 48 hours of hospitalization (i e , in series where mortality rates including these cases were

linically, very nearly nine-tenths of all patients in the treated group escaped such complications. Of the 442 control group patients, 15.8 per cent developed a single thromboembolic complication, but only 9.2 per cent of the 589 treated group patients did so. Whereas 5.3 per cent of the control group developed two thromboembolic complications, only 1.2 per cent of the treated group did so. Similarly, 4.2 per cent of the control group, but only 0.5 per cent of the treated group developed 3 thromboembolic complications. This 0.5 per cent represents only 3 cases, or a total of 9 complications, and 8 of these 9 occurred when patients were not under anticoagulants. Only 0.7 patients per 100 in the control group developed 4 thromboembolic complications, but no patients in the treated group developed this many.

When restated in terms of ratios, the chances of a patient developing one or more thromboembolic complications differed strikingly between the control and treated groups. The chances of developing at least one thromboembolic complication were roughly 1 in 4 among the controls and 1 in 10 among the treated; the chances of [illegible] throm[illegible] 1 in 1[illegible] the tr[illegible], the chances of developing 3 or more thromboembolic complications were 1 in 20 among the controls but only 1 in 200 among the treated, while the chances of developing 4 thromboembolic complications were 1 in 140 among the controls and zero among the treated for this series.

The progressively increasing contrasts with the control group as the count of complications increases is probably explainable on two bases: (1) Anticoagulant therapy was not started in some instances until after one or more thromboembolic complications had occurred and therefore did not influence the first or sometimes even the second complication. (2) Such therapy was probably administered with greater care in many instances where patients had already suffered a previous thromboembolic complication. The zero rate for 4 complications for the treated group must not be assumed to apply to all pathological states since thromboembolic complications are not always controllable with anticoagulants, e.g., in patients with malignancy. In another anticoagulant study (see Appendix A), a patient with cancer of the pancreas and thrombophlebitis developed 6 thromboembolic complications during approximately 6 weeks of anticoagulant therapy, all recurrent episodes of thrombophlebitis. This resistance to anticoagulants in the presence of malignancy has been emphasized by Wright.[257, 258]

The experience with the control group in this analysis may also be used to answer another question: Do some patients have a greater thrombosing tendency than others? When all patients are considered together, the average patient without anticoagulants in this series is seen to have had about a 1 in 4 chance of developing a thromboembolic complication. However, patients who developed at least one complication had 1 chance in 2 or 3 of developing a second complication before the end of the six-week period, and those who had developed at least 2 complications had 1 chance in 2 of developing a *third*.[*] The thrombosing tendency obviously appears to be concentrated in certain types of patients who gradually reveal themselves as the illness progresses. An attempt will be made later in this chapter to identify the type of patient most likely to show a high record of [illegible] *[illegible] complication are*

[*] The above statements do not take into account the unequal periods of exposure involved for the various groups. If allowance were made for the lesser number of days before the end of six weeks which patients who had already developed complications had to develop further complications, the contrasts would probably be increased. The process of actual computation would be complicated since exposure days would have to be weighted according to the level of risk typical of the particular number of days after onset involved.

Again the favorable experience associated with anticoagulants is evident. *Comparisons with other studies thus confirm fully the findings of the present study with respect to the general effectiveness of anticoagulants in reducing thromboembolic phenomena following myocardial infarction.*

Extent of Single and Multiple Complications

The influence of anticoagulants is again evident in the findings with respect to single and multiple thromboembolic episodes. The percentage of cases experiencing no thromboembolic complications, or one, two, three, or four such complications in the control and in the treated groups is shown in Table 94, Appendix F Table 38 and, graphically, in Figure 91. The control group counts are corrected for exceptions in treatment as explained in the preceding section.

The reduction in the incidence of thromboembolic complications in the treated as compared with the control group was consistent in respect to both single and multiple complications, but especially for the latter. Whereas fewer than three-quarters of all patients in the control group escaped thromboembolic complications, as far as could be ascertained

TABLE 94

SINGLE AND MULTIPLE COMPLICATIONS. Percentage of Cases Developing No Thromboembolic Complications or One, Two, Three, or Four Such Complications in the Control and Treated Groups

Number of Complications per Case	Percentage of Cases	
	Control Group[a] (442 Cases)	Treated Group (387 Cases)
None	74.0	89.1
One	15.8	9.2
Two	5.3	1.2
Three	4.2	.5
Four	.7	—
Total cases	100 0	100 0

[a] Corrected for exceptions in treatment. For method of correction, see Appendix B.

SINGLE AND MULTIPLE COMPLICATIONS

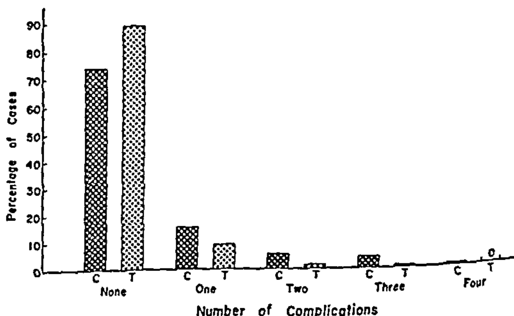


Figure 91. SINGLE AND MULTIPLE COMPLICATIONS: Percentage of cases in control and treated groups developing no thromboembolic complications or one, two, three, or four such complications per case.

:us practically nothing is known of the :ord before anticoagulant therapy began : 224 cases, or more than a third of the :ated group.[1]

One would assume *a priori* that those for hom the risk of complications was most im- inent would be the ones most likely to be laced on anticoagulants promptly. The fol- wing evidence suggests that such selection ctually took place: (1) The treated group ases severely ill at onset and receiving anti- :oagulants were placed on this therapy on *the average a little more than half* a day ear- lier than were cases mildly or moderately ill at onset. (2) Twenty per cent of the severely ill patients received anticoagulants on the first day of their illness as compared with only 15 per cent of those mildly or moder- ately ill. Doubtless more selection actually took place than is revealed by these very rough and inadequate dichotomies for se- verity.

Since severity at onset was closely associ- ated with the complication rate (pages 227–230), this hidden selection would be expected to result in an abnormally low rate for thromboembolic complications in the treated group before the beginning of anticoagulant therapy because of the selective early appli- cation of [illegible] cases. I [illegible] borne [illegible] treated group as a whole contained more cases severely ill at onset than did the con- trol group, the complication rate before the beginning of anticoagulant therapy was only 9.7 complications per thousand days as compared with a corrected rate of 14.5 com- plications for the control group for cor- responding days of their illness (see Table 95).

A test of significance (applied to uncor- rected rates) indicates that this difference is not statistically significant. It is more probable, however, that it is due to the hid- den selection referred to. Unfortunately this interpretation cannot be definitely proved since there is no valid way of correcting the treated group rate for these omitted cases. Under these circumstances, one would not be justified in using the rates before the begin- ning of therapy as a test of the comparability of the control and treated groups with refer- ence to their inherent tendency toward thromboembolic complications because only about two-thirds of the treated group were really represented in the rate and those rep- resented were probably in large part the lower risk cases.

Rates during First Three Days of Therapy

The next available comparison is that for the early period of therapy, that prior to the fourth calendar day of anticoagulants. This early period necessarily represents for most patients an in-between stage during which protection is as yet either completely una- chieved or inadequate. For the patients not receiving heparin supplementation during this period, only 28 per cent of the prothrom- bin readings on the second and third day were at or above the therapeutic minimum of 25 seconds, converted time (see Table 144, Chapter XII). Except for these patients and the relatively few protected with heparin, patients on the remaining days must be as- sumed to have been inadequately or entirely uninfluenced by anticoagulants. The throm- boembolic complication rate is therefore also a transitional one, midway between that characteristic of protection and that charac- teristic of no protection.

The rates for the period represented by these first three calendar days of anticoagu- lant therapy are given in Table 95 and Figure 92. They rest on a sound basis as far as se- lection is concerned since all treated group patients except the 12 who did not [illegible]

[1] The 224 treated group cases who were placed on anticoagulants on the first or second day of their illness were not observed long enough before therapy to obtain any valid complication rate for them for this period; therefore no procedure in- volving a reweighting of such a rate could be used to secure a corrected rate for the total group prior to therapy.

more urgently in need of anticoagulant therapy than are those who have not as yet developed a complication.

Thromboembolic Complication Rates at Various Stages of Therapy

Up to this point, comparisons as to thromboembolic complications between the control and treated groups have been based upon the complications observed over the entire six-week period of observation. In the present section comparisons are attempted for each of the various stages of therapy. It is obvious that the character of the illness following an acute coronary occlusion with myocardial infarction differs from week to week and even from day to day, to a degree independent of the therapy applied. The opportunities for complications of various sorts, including thromboembolic, and the prognosis vary accordingly. To ascertain more precisely the influence of anticoagulant therapy on the occurrence of thromboembolic complications, it was necessary to compare the control and treated groups for exactly comparable periods of time during the course of the present illness.

In order to accomplish this aim, the number of thromboembolic complications was first recorded for each stage of therapy in the treated group. Days of observation were similarly counted for each of these same stages. For increased accuracy, the first day of anticoagulants was divided and one-half considered to fall before anticoagulants and one-half during anticoagulant therapy. To arrive at complication rates for the treated group for the various stages of therapy, these day counts were then divided into the complication counts for corresponding periods and the results stated in terms of number of complications per thousand days.[h]

Since, with few exceptions, patients in the control group did not receive any anticoagulants, but had in other respects the same experience as the treated patients, average rates of thromboembolic complications per thousand days of illness observed were artificially computed for the control group to cover periods of time exactly comparable to those represented by the various stages of therapy in the treated group. This was done by computing the control group complication rates for each day of illness from the first through the forty-second day, and combining these rates in such a way that the weight given to the rate for each day in each composite rate was exactly equal to the number of patients in the treated group receiving the specified type of care on that day of their illness. This process yielded an approximation of the control group complication rate for that portion of the total illness period comparable to the period of therapy for the treated group.

Nevertheless, it could not yield fully comparable data for the two groups for specific therapy periods since many cases in the treated group are represented either very little or not at all in the period before and after therapy. Because of these obvious omissions, one cannot be certain whether differences for these periods are, or are not, due to selection within the treated group.

Rates before Anticoagulant Therapy

This problem of selection is most acute with respect to rates for the control and treated groups for the period before the beginning of therapy. The control group rate is an estimate necessarily based on the weighted daily experience of all control group cases, whereas 93 treated group cases were placed on anticoagulants on the first day of their illness and hence are represented in the treated group rate for the period before anticoagulants with only one-half day each. Another 131 cases in the treated group were placed on anticoagulants on the second day of their illness and are therefore represented in the rate by only one and one-half days.

[h] Those who find it difficult to translate these rates into the more usual types of counts encountered in the literature are referred to the more extended discussion of such rates appearing on p. 272.

ous practically nothing is known of the cord before anticoagulant therapy began r 224 cases, or more than a third of the eated group.[1]

One would assume *a priori* that those for hom the risk of complications was most imminent would be the ones most likely to be laced on anticoagulants promptly. The folowing evidence suggests that such selection actually took place: (1) The treated group cases severely ill at onset and receiving anticoagulants were placed on this therapy on the average a little more than half a day earlier than were cases mildly or moderately ill at onset. (2) Twenty per cent of the severely ill patients received anticoagulants on the first day of their illness as compared with only 15 per cent of those mildly or moderately ill. Doubtless more selection actually took place than is revealed by these very rough and inadequate dichotomies for severity.

Since severity at onset was closely associated with the complication rate (pages 227–230), this hidden selection would be expected to result in an abnormally low rate for thromboembolic complications in the treated group before the beginning of anticoagulant therapy because of the selective early application of anticoagulant therapy to high risk cases. It is interesting that this prediction is borne out by the facts Even though the treated group as a whole contained more cases severely ill at onset than did the control group, the complication rate before the beginning of anticoagulant therapy was only 9 7 complications per thousand days as compared with a corrected rate of 14.5 complications for the control group for corresponding days of their illness (see Table 95).

[1] The 224 treated group cases who were placed on anticoagulants on the first or second day of their illness were not observed long enough before therapy to obtain any valid complication rate for them for this period; therefore no procedure involving a reweighting of such a rate could be used to secure a corrected rate for the total group prior to therapy.

A test of significance (applied to uncorrected rates) indicates that this difference is not statistically significant. It is more probable, however, that it is due to the hidden selection referred to. Unfortunately this interpretation cannot be definitely proved since there is no valid way of correcting the treated group rate for these omitted cases. Under these circumstances, one would not be justified in using the rates before the beginning of therapy as a test of the comparability of the control and treated groups with reference to their inherent tendency toward thromboembolic complications because only about two-thirds of the treated group were really represented in the rate and those represented were probably in large part the lower risk cases.

Rates during First Three Days of Therapy

The next available comparison is that for the early period of therapy, that prior to the fourth calendar day of anticoagulants. This early period necessarily represents for most patients an in-between stage during which protection is as yet either completely unachieved or inadequate. For the patients not receiving heparin supplementation during this period, only 28 per cent of the prothrombin readings on the second and third day were at or above the therapeutic minimum of 25 seconds, converted time (see Table 144, Chapter XII). Except for these patients and the relatively few protected with heparin, patients on the remaining days must be assumed to have been inadequately or entirely uninfluenced by anticoagulants. The thromboembolic complication rate is therefore also a transitional one, midway between that characteristic of protection and that characteristic of no protection.

The rates for the period represented by these first three calendar days of anticoagulant therapy are given in Table 95 and Figure 92. They rest on a sound basis as far as selection is concerned since all treated group patients except the 12 who did not receive

contributed to the rate and most patients were represented on all three calendar days of the period. The actual observed rate for the treated group for this period was 7.0 complications per thousand days of therapy as compared with a corrected rate for the control group of 16.4 complications per thousand days during comparable days of the illness (see Table 95 and Figure 92). The difference is of borderline significance statistically.[j] Thus even within this early period before dicumarol could be fully effective, the decrease in complications associated with the use of anticoagulants was marked.

Rates after the Third Day of Therapy

For the period from the fourth day of anticoagulants through four days after the last dose, or until prothrombin time had returned to normal, the complication rate for the treated

[j] The test was applied to the lesser difference before correction for exceptions in treatment. The difference closely approaches statistical significance when applied to the difference corrected for exceptions in treatment but there are technical objections to the use of the test in this manner.

TABLE 95

COMPLICATION RATES, BY STAGE OF ANTICOAGULANT THERAPY: Number of Thromboembolic Complications and Average Number per Thousand Days of Illness Observed in the Treated Group, by Stage of Anticoagulant Therapy and Corresponding Complication Rates for the Control Group for Exactly Comparable Periods of Time

Stage of Anticoagulant Therapy	Treated Group[a]		Average Number of Thromboembolic Complications per 1000 Days of Illness Observed		
	Number of Days of Illness Observed[b]	Number of Thrombo-embolic Complications	Control Group (Rates artificially computed to cover periods of time exactly comparable to those represented by the various stages of therapy in the treated group)[c]: Computations Based on Data as Reported	Control Group: Computations Based on Data Corrected for Exceptions in Treatment	Treated Group (Rates based on actual data reported)[d]
Before beginning of anticoagulant therapy[e] ...	2,578	25	14.0	14.5	9.7
During first three days of anticoagulant therapy	1,424	10	15.9	16.4	7.0
From the fourth day of anticoagulant therapy through four days after the last dose...	14,496	40	11.3	12 3	2 8
After discontinuance of anticoagulant therapy...	3,356	2	3.9	4.5	.6

[a] Corresponding counts for the control group are not reported since they were artificially computed [illegible] one-half of each [illegible] coagulants" and one-half to "days during the first three days of anticoagulant therapy."

[c] Calculated by computing the control group complication rates for each day of illness from the 1st through the 42nd and combining these rates in such a way that the weight given to the rate for each day in each composite rate was exactly equal to the number of patients in the treated group receiving the specified type of care on that day of their illness.

[d] When the rates for the treated group were adjusted to what they would have been if the age composition of the treated group had been approximately the same as that of the control group, no rate was changed more than one-tenth of 1 complication per 1000 days observed.

[e] Includes time on the first day of anticoagulants before the 1st dose was given and also the total six-week period for the 12 treated cases not receiving anticoagulants because of contraindications

group was only 2.8 per thousand days of anticoagulant therapy as compared with a corrected rate for a comparable period for the control group of 12.3 complications per thousand days observed, or more than four times as many (see Table 95 and Figure 92).

A review of possible explanations in terms other than anticoagulant therapy was unproductive. The difference is highly significant statistically and therefore cannot reasonably be attributed to chance. It cannot be due to a low severity in the treated group since 25.8 per cent of the days covered by the treated group rate (including the first three days of therapy) were for patients severely ill at onset, whereas only 20.7 per cent of the corresponding days covered by the control group estimate were for patients severely ill at onset. The difference also is not due to lack of comparability with respect to age since statistical adjustment for the minor age differences present had no appreciable influence on the contrast. The difference likewise cannot be due to selection through death since the control group lost patients through death during and before the treatment period at a somewhat higher rate than did the treated group (see Table 125, Chapter XI) and such losses, by removing high risk cases from further inclusion in the complication rate, would reduce the control group complication rate more than the treated group rate. Similarly, the tendency of physicians to continue on anticoagulants beyond the usual period of therapy patients with a past record of complications would also operate to the disadvantage of the treated group rate *during* therapy since such patients presumably would still be in more than average danger of developing further complications. Numerous other possible sources of lack of comparability between the control and treated groups also have been reviewed in other sections of the report and found to be of no consequence as an explanation of differences. *It is therefore reasonable to conclude that anticoagulant therapy was responsible for the marked difference between the*

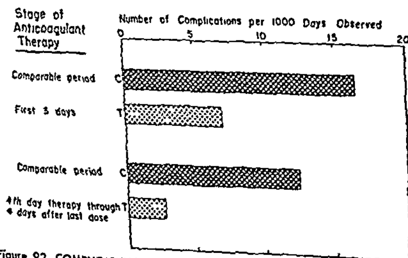


Figure 92. COMPLICATION RATES BY STAGE OF ANTICOAGULANT THERAPY: Average number of thromboembolic complications per thousand days observed in the treated group during the first three days of anticoagulant therapy and from the fourth day of such therapy through four days after the last dose, and corresponding rates for the control group for exactly comparable periods of time.

control and treated group rate of thromboembolic complications during that portion of the period of illness when anticoagulants could have been expected to be effective.

Rates after Discontinuance of Therapy

The comparative rates after the discontinuance of therapy are less meaningful than those for the period of actual therapy, for they were again subject to a selective influence in the direction of mildness such as operated prior to the beginning of therapy. Eighty-six treated group patients did not survive long enough to be observed clinically after the termination of therapy. Anticoagulant therapy was terminated for numerous other patients so late in the six-week period that they were under the influence of anticoagulants until after the termination of the study period. It is reasonable to assume that the attending physicians were selective in the type of patient that they continued on anticoagulants into the fifth and sixth week and that this selection was based on their estimate of the relative risk of complications. Therefore many high risk cases had no after-period and thus could not influence the rate.

That such selection actually took place is suggested by the fact that treated patients who had any record of complications during the six-week period were taken off anticoagulants so late that there was time for only 2.9 days, on the average, of observation after the termination of therapy before the end of the six-week period, whereas those patients who had no record of complications were taken off anticoagulants soon enough to allow for an average of 6.2 days of observation within the study period. Moreover, 69 per cent of the treated group patients who developed one or more complications—an obviously high risk group—are omitted entirely from the rate for the after-therapy period by reason either of death or prolongation of therapy.[k]

[k] The foregoing statements omit treated group cases denied anticoagulants because of medical contraindications.

In view of this selection it is quite understandable that the actual rate for the treated group after the termination of therapy was only 0.6 complications per thousand days (actually only 2 complications), while the rate for the control group not similarly subject to this selective influence was 4.5 complications per thousand days (see Table 95). Some may conclude from this contrast that anticoagulants continue to exert a favorable influence on thromboembolic phenomena even after such therapy has been terminated. Others may conclude that the treated group was inherently one with a low likelihood of thromboembolic complications. Neither conclusion, however, is warranted since cases with a record of complications are disproportionately omitted and underrepresented in this period, as previously demonstrated.

For purposes of evaluating anticoagulants, therefore, it is best to rely in the main on the comparative rates during therapy since these rates are less influenced by selection, and such selection as did occur, namely that toward greater severity, would operate to offset the influence of anticoagulants. Since anticoagulants proved more than equal to counteracting this bias, there can be no doubt as to their protective power.

Types and Locations of Thromboembolic Complications

To provide a simplified general picture of the effects of anticoagulants, the counts quoted thus far have lumped all types of thromboembolic complications together in a single total. While this procedure facilitates statistical evaluation, the clinician may wish to visualize the findings more directly in terms of conditions he is accustomed to observe. In addition, it is interesting to ask whether anticoagulants are equally effective in preventing all types of thromboembolic phenomena. In this section, therefore, the complications observed clinically are presented in detail by type and location. It must be remembered throughout that many

thromboembolic complications are not recognized clinically, even in the best of hands, as will be later demonstrated (see Chapter XIII). Some complications are probably unrecognizable clinically, i.e., may be suspected, but impossible to prove under the circumstances in which they occur.

Classifications Used

The classifications used in this presentation require some introductory comment. Two major groups are used: intracardiac complications, occurring within the heart itself, and extracardiac complications, occurring elsewhere in the body. These major groups are, in turn, subdivided into subcategories as outlined and explained in the following paragraphs:

I. Intracardiac Thromboembolic Complications
(*Secondary Myocardial Infarctions*)

A. *Extensions*—acute infarctions of the myocardium which were diagnosed clinically, which occurred subsequent to the original infarction (i.e., subsequent to the initial infarction for which the patient was hospitalized at the beginning of the present illness), and which were interpreted on the basis of electrocardiographic evidence as being extensions of the original infarction, or, at least, as involving areas of the myocardium contiguous to, or closely approximating, that involved by the original infarction. The presumption is that such extensions resulted from further interference with the blood supply ordinarily maintained through the coronary artery or its branches occluded at the time of the original infarction.

B. *New Infarctions*—acute infarctions of the myocardium which were diagnosed clinically, which occurred subsequent to the original infarction, but which were interpreted on the basis of the electrocardiographic evidence as involving areas of the myocardium distinct from, and usually distant from, that involved by the original infarction. The presumption was that these new areas of infarction resulted from impairment, or cessation of circulation through a coronary artery, or a branch of a coronary artery other than that occluded at the time of the original infarction. This impairment may have arisen from an extension of the primary thrombus, or from an independent thrombus resulting from stagnation of the coronary circulation, ulceration or subintimal hemorrhage in the walls of the vessel, or even from an embolus.

It is not the purpose or intention of this section to discuss at length the various possible mechanisms whereby a coronary artery may be occluded with resulting infarction of the myocardium, especially since it is usually impossible on clinical grounds to distinguish between these various mechanisms. Some consideration will be given this matter in the subsequent section of this monograph devoted to the analysis of cases upon which postmortem examinations were performed (see Chapter XIII).

It is recognized that on clinical grounds, including therein the findings of the electrocardiogram and their interpretation, the diagnosis of secondary myocardial infarction is not infallible. In support of the data as presented in this series, it may be said that the observers might be expected to observe some degree of consistency in making the diagnosis of a secondary myocardial infarction since (a) they were highly trained in the speciality of cardiology, (b) they were subject to a reasonably similar view of the matter, and (c) the criteria upon which their judgment was based, while differing in detail from hospital to hospital, would logically have been fairly consistent with the outlook and practice of current cardiological practice at large.

Undoubtedly the separation of extensions from new infarctions was less consistent than was the diagnosis of some

type of intracardiac complication since this separation was dependent entirely upon the findings of the electrocardiogram and their interpretation. In some instances, electrocardiographic changes were so characteristic as to indicate definitely that not only had a secondary infarction occurred, but that it had involved an area which could be localized rather precisely and its relation to the original infarction estimated with considerable certainty. In other instances, however, the evidence for the localization of the secondary infarction was uncertain and the location assigned to the secondary infarction was, at best, an estimation.

II. *Extracardiac Thromboembolic Complications*

A. *Pulmonary Emboli*—thromboembolic complications involving the lesser circulation, known or presumed to be embolic in character, and accompanied or not by evidence of pulmonary infarction. While thrombosis in situ of the pulmonary arteries is not unknown, it is rare as a complication of myocardial infarction and the vast majority of thromboembolic complications involving the lesser circulation are emboli arising from either (a) the right side of the heart, or (b) the veins of the legs. Such emboli may be small and occlude only minor branches of the pulmonary arteries, or they may be extremely large and occlude the major pulmonary trunks. In the former instance, the clinical effect may be mild; in the latter instance, there may be severe shock or sudden death.

Pulmonary infarction is not by any means the inevitable sequel to pulmonary embolism. When emboli are small and involve only small branches of the pulmonary arteries, collateral circulation through other branches of the pulmonary artery, or through the bronchial arteries may be sufficient to prevent infarction. Furthermore, massive pulmonary embolism may produce sudden death before there is an opportunity for infarction to occur. For these reasons, roentgenography of the chest is not an infallible means of diagnosing the occurrence of a pulmonary embolus.

Similarly, the classical electrocardiographic findings of pulmonary embolism are not encountered in every instance of this condition. They may not appear at any time in the presence of very small emboli, or may not appear before death in instances of massive embolism which produce a prompt demise.

B. *Cerebral Emboli*—cerebrovascular accidents clearly the result of thromboembolism rather than cerebral hemorrhage were sufficiently numerous in this study to be classified separately. In three instances, it was not possible on clinical grounds to be certain whether such a complication represented the effects of an embolus arising in the left side of the heart, or a thrombus developing in situ. In one other instance a thrombosis was definitely diagnosed. All others were believed to be emboli. Evidence collected from the analysis of autopsy material in other sources indicates that the majority of these complications are, in fact, embolic in origin. Transient cerebrovascular episodes which produced neither focal signs, nor residual effects were, in most instances, attributed to temporary cerebral ischemia, arising from cerebral vascular spasm or anoxia from other causes, and were not included among the cases classified in this category.

C. *Peripheral and Visceral Emboli*—all thromboembolic complications involving systemic arteries of the viscera or of the extremities were consolidated into this subcategory. Most of such complications recognized clinically involved the arteries of the extremities, most commonly, of course, the legs. Nearly all were undoubtedly embolic, arising from the left side of the heart, although thrombosis in situ may have occurred in one instance

(mesenteric thrombosis). The possibility of paradoxical embolism was not suggested on clinical grounds in any instance of thromboembolism in this series. Intravascular clots involving arteries other than those to the brain and to the extremities are not commonly recognized clinically, but are identified at postmortem examination. For this reason, very few thromboembolic complications involving visceral structures other than the brain were recognized clinically in this study.

D. *Venous Thrombosis*—included in this category are both phlebothrombosis and thrombophlebitis which are not, in our opinion, clearly separable entities. Thrombophlebitis may be considered as primarily an inflammatory lesion of the veins characterized by definite and often incapacitating local signs and symptoms and usually by moderate or severe systemic symptoms of a nonspecific nature. The classical example of such a lesion is the full-blown acute iliofemoral thrombophlebitis. From the same viewpoint, phlebothrombosis is the relatively benign, primarily thrombotic lesion of the veins, characterized by mild to moderate local symptoms (there may be none at all) and signs and not accompanied as a rule by any systemic manifestations unless complications occur. The classical example of such a lesion is phlebothrombosis of the deep plantar veins, or of the deep veins of the calf.

It is to be emphasized that the term "benign" as applied to phlebothrombosis is misleading and applies only to the mild local manifestations and the relative absence of systemic manifestations in uncomplicated cases. The local lesion may extend to involve other deep or superficial veins and may exhibit eventually every evidence of an acute inflammatory process. More important is the fact that the so-called "benign phlebothrombosis" is particularly prone to serve as the origin of pulmonary emboli, some of which may be fatal. Most instances of acute thrombophlebitis are diagnosed with some certainty because of the obvious symptoms and signs of acute inflammation associated with them. Many instances of phlebothrombosis are unrecognized because of the involvement of deeply situated veins and the relatively mild local manifestations. Even autopsy statistics do not clarify the matter inasmuch as it is unusual in routine postmortem examinations to include careful dissection of the deep venous system of the legs throughout their length.

Findings in This Study with Regard to Type of Complication

Counts of these various types of complications for the control and treated groups indicated that the 442 cases in the control group suffered clinically 40 extensions of the initially infarcted area, 25 infarctions of new areas of the myocardium, 48 pulmonary emboli, 20 cerebral emboli (or thrombi), 11 peripheral and visceral emboli (or thrombi), and 28 venous thromboses. The peripheral and visceral emboli included 4 emboli to the arteries of the legs, 4 in the aorta (including 1 saddle embolus at the bifurcation of the abdominal aorta), 1 in the right axillary artery, 1 in the mesenteric artery (possibly a thrombus), and 1 in the renal artery. All venous thromboses whose location was reported were in the legs.

The 589 cases in the treated group suffered 19 [illegible] inf[illegible] 28 [illegible], 4 cerebral emboli (of which 1 was possibly a thrombus), 3 peripheral and visceral emboli, and 12 venous thromboses, of which 10 were in the leg, 1 in the left arm, and 1 in the left jugular vein. The peripheral and visceral emboli in the treated group consisted of 2 renal emboli and 1 embolus in the arm.

The rates corrected for exceptions in treatment and stated in terms of number per hundred cases are given in Table 96 and are shown graphically in Figure 93. Full details

type of intracardiac complication since this separation was dependent entirely upon the findings of the electrocardiogram and their interpretation. In some instances, electrocardiographic changes were so characteristic as to indicate definitely that not only had a secondary infarction occurred, but that it had involved an area which could be localized rather precisely and its relation to the original infarction estimated with considerable certainty. In other instances, however, the evidence for the localization of the secondary infarction was uncertain and the location assigned to the secondary infarction was, at best, an estimation.

II. *Extracardiac Thromboembolic Complications*

A. *Pulmonary Emboli*—thromboembolic complications involving the lesser circulation, known or presumed to be embolic in character, and accompanied or not by evidence of pulmonary infarction. While thrombosis in situ of the pulmonary arteries is not unknown, it is rare as a complication of myocardial infarction and the vast majority of thromboembolic complications involving the lesser circulation are emboli arising from either (a) the right side of the heart, or (b) the veins of the legs. Such emboli may be small and occlude only minor branches of the pulmonary arteries, or they may be extremely large and occlude the major pulmonary trunks. In the former instance, the clinical effect may be mild; in the latter instance, there may be severe shock or sudden death.

Pulmonary infarction is not by any means the inevitable sequel to pulmonary embolism. When emboli are small and involve only small branches of the pulmonary arteries, collateral circulation through other branches of the pulmonary artery, or through the bronchial arteries may be sufficient to prevent infarction. Furthermore, massive pulmonary embolism may produce sudden death before there is an opportunity for infarction to occur. For these reasons, roentgenography of the chest is not an infallible means of diagnosing the occurrence of a pulmonary embolus.

Similarly, the classical electrocardiographic findings of pulmonary embolism are not encountered in every instance of this condition. They may not appear at any time in the presence of very small emboli, or may not appear before death in instances of massive embolism which produce a prompt demise.

B. *Cerebral Emboli*—cerebrovascular accidents clearly the result of thromboembolism rather than cerebral hemorrhage were sufficiently numerous in this study to be classified separately. In three instances, it was not possible on clinical grounds to be certain whether such a complication represented the effects of an embolus arising in the left side of the heart, or a thrombus developing in situ. In one other instance a thrombosis was definitely diagnosed. All others were believed to be emboli. Evidence collected from the analysis of autopsy material in other sources indicates that the majority of these complications are, in fact, embolic in origin. Transient cerebrovascular episodes which produced neither focal signs, nor residual effects were, in most instances, attributed to temporary cerebral ischemia, arising from cerebral vascular spasm or anoxia from other causes, and were not included among the cases classified in this category.

C. *Peripheral and Visceral Emboli*—all thromboembolic complications involving systemic arteries of the viscera or of the extremities were consolidated into this subcategory. Most of such complications recognized clinically involved the arteries of the extremities, most commonly, of course, the legs. Nearly all were undoubtedly embolic, arising from the left side of the heart, although thrombosis in situ may have occurred in one instance

onary emboli as compared with 28 per cent total complications for the control group.

Before one can conclude that anticoagunts are more effective in preventing cereral, peripheral, and visceral emboli and less fective with pulmonary emboli, one must sk whether this relationship is spurious and ue merely to the fact that the latter norally occur at periods of the illness not adeuately protected by anticoag[illegible]

[illegible]

ach type of complication occurring during the first week of the illness and the average number of days after the original attack that they occurred in control cases. Data from the control group only are used for this purpose since the biological pattern in the absence of anticoagulant therapy is the point at issue.

From this tabulation, it is immediately evident that pulmonary emboli were particularly frequent during the first week of the illness. This fact undoubtedly provides the explanation for the relatively lower effectiveness of anticoagulants with this type of complication, namely, that these complications often occurred before anticoagulants could be fully effective. *Adequate protection against pulmonary emboli requires more prompt and more complete protection with anticoagulants early in the illness than was the typical practice in the present study.*

In passing, it is interesting to speculate as to the reason for the relatively high proportion of pulmonary emboli occurring in the first week of the illness. Of 27 pulmonary emboli occurring in the control and treated groups in the first week, only one was preceded by a clinically diagnosed venous thrombosis and only one of these emboli occurred in a patient reported to have any history of thrombophlebitis. If these emboli originated in the legs, therefore, the leg thromboses were almost uniformly undiagnosed. On the other hand, the evidence does not support the inference that these emboli

TYPE AND LOCATION OF COMPLICATIONS

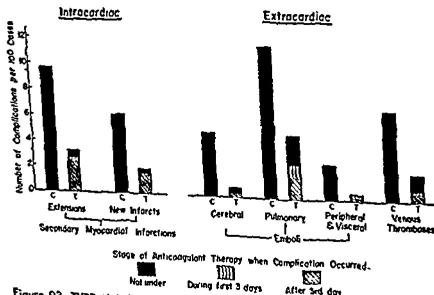


Figure 93. TYPE AND LOCATION OF COMPLICATIONS: Average number of various types of intracardiac and extracardiac thromboembolic complications occurring per hundred cases in the control and treated groups and status of anticoagulant therapy at time complication developed.

appear in Appendix F, Table 39. Every type of complication showed markedly lower rates in the treated group. When the differences were tested for significance in the manner described in Appendix C, they were found highly significant statistically in the case of intracardiac complications, cerebral emboli, and all other types combined, and statistically significant in the case of pulmonary emboli.

TABLE 96

TYPE AND LOCATION OF COMPLICATIONS: Average Number of Thromboembolic Complications of Various Types and Locations per Hundred Cases in the Control and Treated Groups

Type and Location of Complication	Average Number of Thromboembolic Complications per 100 Cases	
	Control Group[a] (442 Cases)	Treated Group (589 Cases)
	Intracardiac Thromboembolic Complications	
Secondary myocardial infarctions:		
Extensions	9.7	3.2
New infarctions	6.1	1.9
Total intracardiac complications	15.8	5.1
	Extracardiac Thromboembolic Complications	
Emboli:		
Pulmonary	11.6	4.8
Cerebral[b]	4.9	.7
Peripheral and visceral[c]	2.7	.5
Venous thromboses	6.8	2.0
Total extracardiac complications	26.0	8.0
Total, all thromboembolic complications	41.8	13.1

[a] Data are corrected for exceptions in treatment. For explanation of method of correction, see Appendix B.

[b] Category includes 2 complications in the control group and 1 complication in the treated group which may have been cerebral thromboses, and 1 complication in the control group diagnosed definitely as a thrombosis.

[c] Category includes 1 complication in the control group which may have been a mesenteric thrombosis.

To explore the question of whether reductions were relatively more substantial in some categories than in others, the control group experience (after correction for exceptions in treatment) may be considered the "expected" figure and the treated group rate then stated as a percentage of this "expected" level. When measured in these terms, admittedly approximate,[1] the least reduction was found to have occurred in the case of pulmonary emboli, which showed a treated group rate 41 per cent of the "expected." Myocardial extensions ranked next with a reduction to 33 per cent of the "expected." The greatest reductions occurred for cerebral and for peripheral and visceral emboli, which were 14 and 19 per cent of the "expected" figure respectively. The other reductions, stated as percentages of the "expected" figures, were intermediate in amount, namely 29 per cent for venous thromboses and 31 per cent for new myocardial infarctions. Taken as a whole, extracardiac complications showed almost exactly the same reductions as did intracardiac—31 and 32 per cent of the "expected" rates respectively.

These differences in the relative reductions associated with anticoagulant therapy also affect the proportion of total complications falling in various categories. Less than 10 per cent of the treated group complications were cerebral, peripheral, or visceral emboli as compared with 18 per cent of the control group complications. Conversely, 36 per cent of the treated group complications were pul-

[1] This procedure may involve substantial error since each difference between control and treated figures is subject to the usual fluctuations of random sampling, as are also the separate figures for each group. Therefore, when this procedure is used here and elsewhere, deductions should be conservative and guarded.

or (2) *that they prevent the formation of mural thrombi* Autopsy evidence indicating a significant reduction under anticoagulants in the average number of heart chambers with mural thrombi at autopsy supports the latter interpretation (see Chapter XIII).

Finally the data may be examined from the point of view of when the complications occurred in relation to the various stages of ticoagulant therapy for the treated group. hile comparisons thus far in this section ive been concerned mainly with the total x-week period for both groups, Appendix , *Table 39* also reports the number of comlications per 100 cases occurring before the eginning of anticoagulants, during the first ; days of anticoagulant therapy, and after he third day. Figure 93 also shows these ame components graphically. Since these component rates apply only to portions of the total period, they cannot fairly be compared with a control group rate that applies to a total six-week period.[m]

It is noteworthy that only about a third of the extracardiac complications occurred after the third day of anticoagulant therapy, the period of potentially effective therapy with dicumarol, whereas 80 per cent of the intracardiac complications occurred after the third day. This observation is consistent with the finding that all "true" failures of anticoagulant therapy (i e., complications occurring when times for 3 days or more had been at 30 seconds or more or 16 per cent or less) were intracardiac complications These data would seem to suggest that perhaps anticoagulants were less effective in controlling intracardiac complications than extracardiac. Perhaps the explanation for this observation lies *in the fact* that only about three-fourths of the intracardiac complications found at autopsy were clearly thrombotic in origin[a] In spite of this fact, however, substantial differences were observed. Perhaps this favorable result was facilitated by the fact that intracardiac complications developed on the average later in the illness than embolic phenomena; thus, the risk of such complications would be greater during the typical period of anticoagulant therapy when protection could be effective.

In view of these complexities, one can conclude only that (1) *anticoagulants effect substantial reductions in all types of complications whether intracardiac or extracardiac, and* (2) *they seem particularly effective in reducing emboli originating in mural thrombi.* The reductions achieved in the case of intracardiac complications and pulmonary *emboli were* of lesser magnitude but the significance of these differences is open to doubt since these complications typically occur at selected times during the illness that may affect relative rates and since recognition of complications clinically varies widely by site and type.

Findings on Embolic Phenomena in Other Studies

An inclusive review of the specific types of thromboembolic complications found in the *19 other* controlled studies reviewed in Table 93 cannot be presented because of numerous differences among studies in reporting procedures and the frequent omission of essential details. For comparative purposes, however, it is appropriate to mention several attempts to survey the literature for data on the incidence of clinically diagnosed embolic phenomena complicating myocardial infarction in the absence of anticoagulant therapy that appeared shortly after the in- [illegible] series, 11.5 per cent had exhibited peripheral emboli or *infarctions* clinically. They also demonstrated with autopsy data that such complications were grossly

[m] For such comparisons special computations are needed such as were the basis of data in Table 95.

[a] Of 24 extensions and new secondary infarctions found at autopsy, 17 were clearly due to thrombi, 2 were ascribed to an arteriosclerotic plaque producing occlusion, 3 were caused by advanced arteriosclerosis, 1 was due to an old occlusion plus marked arteriosclerosis, and 1 was of unknown etiology.

originated in large number from mural thrombi since (1) among cases receiving no anticoagulants, the left heart chambers at autopsy were found to have thrombi 3 times as often as the right heart chambers (see Table 159, Chapter XIII), and (2) there were twice as many pulmonary emboli during the first week of the illness as emboli to all parts of the systemic circulation combined (for the total period, 1.5 times as many). It seems clear that these pulmonary emboli could not have originated mainly from mural thrombi in the right heart chambers. They must rather have been either (1) thrombi developing in the lungs themselves (not emboli) or (2) emboli originating in undiagnosed thrombi in other parts of the venous circulation. The latter seems the more probable since no lung thrombi were found at autopsy that had produced infarctions and those that did not produce infarctions usually would have remained undiagnosed clinically. Further support of this deduction is found in Byrne and O'Neil's report[16] that of 130 cases of fatal pulmonary embolism studied at autopsy, 91 per cent showed evidence that the emboli had come from the leg veins. The majority had positive signs of phlebitis. These facts re-emphasize once more *the unpredictable nature of complications and make clear the need for the routine administration of anticoagulants in spite of the absence of warning signals.*

Table 97 also indicates that cerebral, peripheral, and visceral emboli also occurred relatively early on the average although a lower proportion occurred in the first week than in the case of pulmonary emboli. Intracardiac complications took a middle position with respect to time of occurrence and clinically diagnosed venous thromboses occurred on the average later than other types. The very high reduction achieved with anticoagulant therapy in the case of cerebral, peripheral, and visceral emboli are therefore the more remarkable since they were achieved in spite of the typical tendency of these complications to occur early in the illness (one-half before the tenth day). These observations suggest two possibilities: (1) *that anticoagulants are particularly effective in controlling embolization from mural thrombi,*

TABLE 97

TIME OF ONSET OF COMPLICATIONS, BY TYPE: Percentage of Total Thromboembolic Complications of Various Types in the Control Group That Occurred during the First Week of the Illness and Mean and Median Number of Days after the Onset of the Illness on Which Each Type of Complication Occurred

Type of Complication	Control Group (442 Cases)			
	Number of Complications with Time of Onset Reported*	Percentage of Complications Occurring in First Week of Illness	Average Number of Days after Onset of Illness Complication Occurred	
			Mean	Median
Intracardiac complications	64	22	14	12
Pulmonary emboli	48	38	12	9
Cerebral, peripheral, and visceral emboli[b]	31	29	11	8
Venous thromboses	28	*18*	*17*	*16*

... factors render such ... is excluded from

[b] Includes 3 complications which may have been thromboses and 1 complication [illegible]agnosed definitely as a thrombosis.

This pattern was repeated in the treated group but at a lower level. The average number of thromboembolic complications per 100 cases increased from the first to the second week, from 3.1 to 4 9 and then fell off to 2.3, 1.0, 0.8 and 0.8 during the ensuing four weeks. Again, the peak incidence occurred during the second week. The rates during the first and third weeks were roughly equal but again at a level somewhat less than that of the second week (the former two-thirds and the latter, about one-half of the second-week rates). The incidence during each of the last three weeks was essentially the same, again at a level about one-fifth that of the peak, or second week. This peak in the second week in both groups is of special interest since it coincides approximately with the onset of what Beaumont, Chevalier and Lenègre[17] have termed the period of late hypercoagulability which they believe starts on the eight or tenth day and lasts usually a few eks.

When the treated group rates are compared with the corresponding corrected rates for the control group, they are found never to have exceeded about a third of this "expected" rate and in the third and fourth week were well under a third. The differences between these rates for each week from the first through the fourth were highly significant statistically when tested by the procedures described in Appendix C. It may be concluded therefore that *anticoagulants were associated with a significant reduction in the incidence of complications during the first four weeks of the illness.* The savings were the greatest during the third and fourth week when the largest proportion of patients were under anticoagulant therapy and prothrombin levels were most nearly adequate (see *Appendix F, Table 77*). The reductions in the fifth and sixth week were proportionately similar but were not tested for significance because of the low number of complications involved.

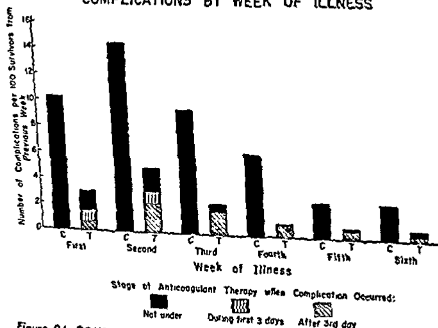


Figure 94. COMPLICATIONS BY WEEK OF ILLNESS: Average number of thromboembolic complications per hundred survivors from the previous week in control and treated groups and status of anticoagulant therapy at time complication developed, by week of illness.

underreported. Doscher and Poindexter[11] also reviewed 1927 cases from the literature, plus 414 in their own series, and found that of the combined total of 2341 cases, 10.8 per cent were reported to have shown "embolic phenomena." Mintz and Katz[11] also discussed thromboembolism following coronary occlusion with myocardial infarction at some length and referred to the reports of a number of previous observers. In the series of 572 cases reported by Mintz and Katz, 9.9 per cent developed thromboembolic complications, most of which were emboli. These reports served to focus attention on the importance of thromboembolism in myocardial infarction.

Comparisons with the present study indicate that all these figures from the literature are below the percentage of control group cases showing extracardiac arterial thromboembolic phenomena clinically in the present series, namely, 13.6 per cent. This difference can probably be explained on the basis of underreporting due to lack of full awareness of the problem in the period prior to the introduction of anticoagulants. In spite of this probable underreporting, however, these pooled figures from the literature are all higher than the corresponding 5.1 per cent figure for the treated group in the present study. *Thus, a substantial reduction associated with anticoagulant therapy is evident regardless of the group selected for use in control comparisons.*

Incidence of Complications by Week of Illness

When the data are analyzed from yet another approach, they can be used to answer such clinically important questions as: How long after an attack of coronary thrombosis with myocardial infarction does the risk of thromboembolic complications remain high? When is the risk the greatest? How soon should anticoagulants be started? How long should anticoagulant therapy be continued? To throw light on these issues, the average number of thromboembolic complications per 100 survivors was calculated week by week during the six-week period of observation. The resulting data are summarized in Table 98 and shown graphically in Figure 94. Full details are given in Appendix F, Table 40. Time was computed throughout from the *date of onset* of the attack and *not* from the date of hospitalization, a specification that is important when comparisons are made with other studies.

Among cases in the control group, the average number of thromboembolic complications per 100 cases increased from 10.2 during the first week to 14.3 during the second week and then fell off to 9.4, 6.2, 2.7, and 2.7 during the ensuing four weeks. *Thus the peak incidence occurred during the second week of the illness.* The incidence during the first and third weeks was roughly equal, in each case about two-thirds that of the second week. The incidence during the final two weeks was identical and only one-fifth that of the peak, or second week.

TABLE 98

COMPLICATIONS, BY WEEK OF ILLNESS

Average Number of Thromboembolic Complications per Hundred Survivors from the Previous Week in the Control and Treated Groups, by Week of Illness

Week of Illness	Average Number of Thromboembolic Complications[a] per 100 Survivors[b] at Beginning of Week	
	Control Group[c]	Treated Group
First week	10.2	3.1
Second week	14.3	4.9
Third week	9.4	2.3
Fourth week	6.2	1.0
Fifth week	2.7	.5
Sixth week	2.7	.8

[a] Counts exclude 5 complications in the control group and 7 complications in the treated group for which the date of occurrence is unknown.

[b] For number of survivors at the beginning of each week on which these rates are based, see Appendix F, Table 40.

[c] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

with similar data for bleeding episodes as a basis for determining a recommended therapeutic range for prothrombin times. To round out the picture for thromboembolic complications, Figure 95, based on Table 10, Chapter XII, summarizes the findings d is included here.

Examination of this figure leads to the following deductions: (1) all prolongations of rothrombin times during dicumarol therpy, including minimal ones, were associated n the average with substantial reductions in hromboembolic complications in comparion with the control group rates for a coresponding period of the illness, (2) dicumarol therapy did not succeed in completely eliminating thromboembolic complications even at prolongations involving substantial risk of hemorrhage, (3) the full advantages of anticoagulant therapy were achieved with prothrombin times beginning at times of 25 to 29 seconds and no further reduction in complications was associated with prolongations beyond this level, not even with times longer than 50 seconds, (4) complication rates for times of less than 25 seconds (24 per cent or more prothrombin activity) were consistently about twice as high as rates for times of 25 seconds or more. In interpretation, no weight should be given either to minor fluctuations which may be due to chance or errors in the laboratory or conversion technics used, or to the apparent drop in complications below 20 seconds. This latter drop is perhaps spurious since days under heparin were omitted and the patients represented by these rates, typical of the initial stages of therapy, were thus those not selected for initial heparin supplementation on these days. It is possible, therefore, that

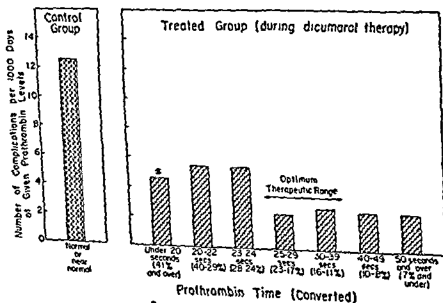


Figure 95. COMPLICATION RATES BY PROTHROMBIN LEVELS: Average number of thromboembolic complications per thousand days patients were maintained at various prothrombin levels from the second day of dicumarol therapy through four days after the last dose (weighted averages of weekly rates) for all patients in the total sample receiving dicumarol and the corresponding rate for the control group for an approximately comparable period of the illness.

From the high rate during the first week in the control group, it may be concluded further that *anticoagulants should be begun as soon as possible after the attack and that adequate prothrombin levels should be produced in the patient as rapidly as possible.* The consequences of delay were apparent during the first two weeks in the treated group when 19 complications occured in patients who were *not* under anticoagulants and 10 more, during the first three days of dicumarol therapy in patients who were not receiving heparin supplementation at the time of the complication (see Table 122, Chapter X). If anticoagulants had been more promptly administered and heparin supplementation given, many of these complications would probably have been prevented.

Since the number of complications remained high in the control group through the fourth week, it may be concluded further that *anticoagulant therapy should be continued for at least four weeks after the initial attack.* Under some circumstances four weeks of anticoagulant therapy may be inadequate, as for example when complications have developed during therapy. It is therefore also recommended that *all cases developing thromboembolic complications during the illness be continued on anticoagulants at least four weeks after the day of the last thromboembolic complication.*

Sometimes four weeks of therapy are inadequate even when no complications have occurred during therapy, as the following case will illustrate. A 41-year old male, who had already had two myocardial infarctions prior to the present attack, was kept on dicumarol for the recommended period of four weeks beginning with the first day after his attack. His recovery proceeded without complications and he received his last dose of dicumarol (50 mg.) on the 29th day of his illness. On the 34th day, when his prothrombin time had returned to normal and he appeared to be doing well, he developed marked respiratory difficulty, became cyanotic and pulseless, failed to respond to drugs and an intracardiac injection, and died within 15 minutes.* He was found at autopsy to have developed a fresh septal infarction from a thrombosis. As this example demonstrates in concrete terms, anticoagulants have no protective effect after they have been withdrawn and prothrombin times have returned to normal. They must be continued whenever the risk is felt to be great.

Long-term dicumarol therapy with ambulatory patients has proved practical, safe and rewarding provided careful professional supervision and reliable laboratory control are available.[9, 45, 65, 126, 161, 227, 253, 301] *All patients with a record of repeated myocardial infarction should therefore be considered for long-term anticoagulant therapy.*

Incidence of Complications by Prothrombin Levels

The reports on complications also lend themselves to answering a further question of great therapeutic importance, namely: What prothrombin levels must be maintained to give maximum protection against thromboembolic complications? To provide an answer, all complications occurring at known prothrombin levels from the second day of dicumarol therapy through four days after the last dose were analyzed according to the prothrombin levels reported for the day on which symptoms first appeared. These counts were converted into incidence rates by dividing them by the number of days patients were known to have been kept at these levels, the results being stated in terms of the number of complications per thousand days at each level. The findings and specifications are given in detail in Chapter XII where they are used in conjunction

* The occurrence of this complication such a short time after the termination of anticoagulants may have been a pure coincidence. There was no evidence of any abnormally high rate in the treated group after the termination of therapy (see Table 95). Further comment on complications after the termination of therapy was included in the report on Tromexan (see Appendix A).

rol group shows an increase over the preceding one. The corresponding rates for the reated group also show some increase with ge but most of the rates remain fairly contant until the eight decade.

The upward trends were in general moderte in slope and presented certain irregularies. Nevertheless, the picture was relatively onsistent and seemed medically reasonable n view of the known deterioration in the ...

vas characteristic of the patients in this eries.

A further statistical comparison of the iverage number of complications per hunlred cases among control group patients 60 rears of age and over with the ...

ugher in the older age group. *It would therefore appear wise to practice clinically on the basis of the hypothesis that anticoagulant protection is especially needed by older persons.*

One may also return to these same tables with a second significant question, namely: Are anticoagulants equally effective with all age groups? To answer this question the average number of complications per hundred cases in the treated group may be stated as a percentage of the control group, or "expected" rate The percentages resulting from such a comparison are in sequence from the fifth to the eight decade as follows: 38, 31, 26 and 40 per cent It will be noted that relatively greater reductions were achieved in the middle age groups

Similarly, comparison of thromboembolic developments in the control and treated groups within each major ten-year age group yielded results that conform consistently to this same pattern The differences in case rates and in the average number of complications per hundred cases between the control and treated ...

have ...

since ...

significant for each type of rate for ages 50 to 59 and 60 to 69,[e] but only of "borderline" significance for ages 40 to 49 and 70 to 79.[f] The higher levels of significance for the middle age groups result both from the greater contrasts with "expected" rates for these age groups already mentioned and from the

TABLE 100

COMPLICATIONS ON A DAY-RATE BASIS, BY AGE: Average Number of Thromboembolic Complications per Thousand Days Observed in the Control and Treated Groups and Average Number per Thousand Days of Anticoagulant Therapy in the Treated Group, by Age

Age Group	Average Number of Thromboembolic Complications per 1000 Days of Given Type[a]		
	Control Group (Rate per 1000 Days of Illness Observed)[b]	Treated Group	
		Rate per 1000 Days of Illness Observed	Rate per 1000 Days of Anticoagulant Therapy
Under 50	8.7	3.0	2.9
50–59	10 8	3.3	2.5
Total under 60	10 1	3.2	2 6
60–69	14 3	3.4	3.5
70 and over	15.0	5.4	4.3
Total 60 and over	14.5	4.0	3.8
All ages[c]	11.9	3.5	3.1

[a] Computed from number of days observed for each subgroup as given in Appendix F, Table 58 less corrections for exceptions in treatment for the four control group age groups as follows (in sequence from youngest to oldest): 8 days, 11 days, 151 days, and 51 days. Counts of thromboembolic complications are given in Appendix F, Table 42.

[b] Data are corrected for exceptions in treatment For method of correction, see Appendix B.

[c] Includes cases of unknown age.

[e] Three out of four tests for the middle age ranges yielded a "highly significant" classification. For procedures, qualifications, etc., see Appendix C.

[f] The age group 40 to 49 achieved a "borderline" significance rating for the case rate comparison only when the direction of the difference was taken into account.

these patients may have been a group of below average risk, though statistical confirmation of this hypothesis has not been attempted.

A further tabulation, also presented in detail in Chapter XII, gives evidence that prothrombin times on the days immediately preceding are probably also a factor in the onset of complications. These data showed *a lower complication rate for periods when three successive days had been 30 seconds or more than for days at this level that had been preceded by one or more days at lower levels.*

From these various findings it follows that *the best protection feasible against thromboembolic complications is achieved when prothrombin times are kept consistently at levels sufficiently above 25 seconds (23 per cent or less prothrombin activity) to assure that the patient does not drop below this level at any time day or night throughout the prescribed period of therapy.* The upper limits that must be observed to prevent excessive risk of bleeding are discussed in Chapter XII.

VARIATIONS IN RATES BY TYPE OF PATIENT

The remainder of this chapter is devoted to a consideration of the effect of various characteristics of patients on the incidence of thromboembolic complications and on the effectiveness of anticoagulant therapy. The findings will help to delineate the types of patients most likely to develop complications and the probability that anticoagulants can be of assistance in protecting them from untoward thromboembolic developments.

Age in Relation to Complications

Of various describable characteristics, age is one of the most fundamental for research on myocardial infarction. The basic counts on complications by age are given in Tables 99 and 100 and in Figures 96 and 97. The detailed counts appear in Appendix F, Tables 41 and 42.

These presentations are designed first of all to answer the question: Is there any difference in the risk of thromboembolic complications at different age levels? The control group rates suggest that there is. In the data for this group a fluctuating upward trend is apparent by age in the percentage of cases developing thromboembolic complications and in the average number of such complications per 100 cases. In rates based on the average number of complications per thousand days observed,[p] every decade in the con-

[p] In corrected day rates quoted throughout the remainder of this chapter, the base day counts

TABLE 99

COMPLICATIONS, BY AGE: Percentage of Cases in the Control and Treated Groups Developing One or More Thromboembolic Complications and Average Number of Such Complications per Hundred Cases, by Age

Age Group	Total Cases Observed		Percentage of Cases Developing One or More Thromboembolic Complications		Average Number of Thromboembolic Complications per 100 Cases	
	Control Group	Treated Group	Control Group	Treated Group	Control Group[a]	Treated Group
Under 40	9	17	—[b]	*11.8*	—[b]	*11.8*
40–49	72	94	22.2	10.6	30.4	11.7
50–59	152	218	27.6	10.1	41.8	12.8
60–69	133	172	24.1	10.5	46.2	12.2
70–79	70	72	31.4	13.9	45.0	18.1
80–89	5	14	—[b]	*14.3*	—[b]	*14.3*

Note: *Italics are used when percentages and rates quoted have less than 30 cases as a base since chance factors render such figures particularly unstable.*

[a] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

trol group shows an increase over the preceding one. The corresponding rates for the treated group also show some increase with ... but most of the rates remain fairly ...

... in slope and presented certain irregularities. Nevertheless, the picture was relatively ...nsistent and seemed medically reasonable ... view of the known deterioration in the ...ndition of the arterial walls with advancing ...e and the increase with age in the proportion of patients showing heart failure which ...as characteristic of the patients in this ...ries.

A further statistical comparison of the average number of complications per hundred cases among control group patients 60 years of age and over with the corresponding average for patients under 60 also showed the number of complications to be significantly higher in the older age group. *It would therefore appear wise to practice clinically on the basis of the hypothesis that anticoagulant protection is especially needed by older persons.*

One may also return to these same tables with a second significant question, namely: Are anticoagulants equally effective with all age groups? To answer this question the average number of complications per hundred cases in the treated group may be stated as a percentage of the control group, or "expected" rate. The percentages resulting from such a comparison are in sequence from the fifth to the eight decade as follows: 38, 31, 26 and 40 per cent. It will be noted that relatively greater reductions were achieved in the middle age groups.

Similarly, comparison of thromboembolic developments in the control and treated ...

... pattern. The differences in case rates and in the average number of complications per hundred cases between the control and treated groups were found statistically significant for each type of rate for ages 50 to 59 and 60 to 69,[e] but only of "borderline" significance for ages 40 to 49 and 70 to 79.[f] The higher levels of significance for the middle age groups result both from the greater contrasts with "expected" rates for these age groups already mentioned and from the ...

have been corrected for exceptions in treatment since without these exceptions the days observed would have been reduced through further deaths.

TABLE 100

COMPLICATIONS ON A DAY-RATE BASIS, BY AGE: Average Number of Thromboembolic Complications per Thousand Days Observed in the Control and Treated Groups and Average Number per Thousand Days of Anticoagulant Therapy in the Treated Group, by Age

Age Group	Average Number of Thromboembolic Complications per 1000 Days of Given Type[a]		
	Control Group (Rate per 1000 Days of Illness Observed)[b]	Treated Group: Rate per 1000 Days of Illness Observed	Treated Group: Rate per 1000 Days of Anticoagulant Therapy
Under 50	8.7	3.0	2.9
50-59	10.8	3.3	2.5
Total under 60	10.1	3.2	2.6
60-69	14 3	3.4	3.5
70 and over	15.0	5.4	4.3
Total 60 and over	14.5	4.0	3.8
All ages[c]	11.9	3.5	3.1

[a] Computed from number of days observed for each subgroup as given in Appendix F, Table 58 less corrections for exceptions in treatment for the four control group age groups as follows (in sequence from youngest to oldest): 8 days, 11 days, 151 days, and 51 days. Counts of thromboembolic complications are given in Appendix F, Table 42.

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[c] Includes cases of unknown age.

[e] Three out of four tests for the middle age ranges yielded a "highly significant" classification. For procedures, qualifications, etc., see Appendix C

[f] The age group 40 to 49 achieved a "borderline" significance rating for the case rate comparison only when the direction of the difference was taken into account.

larger samples available of persons of these ages.

From these findings, it seems reasonable to conclude that (1) *anticoagulant therapy is associated with important reductions in the risk of thromboembolic complications at all age levels commonly suffering from myocardial infarction*, and (2) *anticoagulants are possibly slightly more effective with persons from 50 through 69 years of age than with persons in the more extreme age groups*. The medical explanation for this latter finding is not apparent.

The data may be refocused once more to answer a third question: Do anticoagulants eliminate the rising risk of complications with increase in age? Pertinent data on this question may be found in Table 100 which presents for the treated group the average number of complications occurring during anticoagulant therapy per thousand days of such therapy. The answer seems clear. The day rate for persons 60 years and over during therapy was 3.8 complications per thousand days of therapy as compared with a rate of 2.6 for persons under 60. The 46 per cent increase in the older treated group is surprisingly similar to that for the control group, in which persons 60 and over showed 40 per cent more complications per thousand days of illness observed than did persons under 60. Thus, in the present study, although the actual reductions due to therapy were striking, *anticoagulants did not succeed in eliminating the apparent upward trend in complication rates with increasing age.*

These same questions may be repeated with profit for each type of complication separately. To what extent, for example, does the overall increase in the risk of complications with advance in age hold true also for each type of thromboembolic compli-



Figure 96. CASES DEVELOPING COMPLICATIONS, BY AGE: Percentage of cases in control and treated groups developing one or more thromboembolic complications, by age and status of anticoagulant therapy at time of first complication.

n considered separately? The findings of s study with respect to specific types of ... in Appendix F

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e to small numbers in sub...ories, the e data have been consolidated into two oups: under 60 and 60 and over.

In the control group, which was *on* the hole uninfluenced by anticoagulants, the

...

r the older age group except venous thromoses, but for pulmonary emboli the increase the control group was so small as not to e discernable graphically. It would appear hat *age affects unfavorably the incidence of ... types of thromboembolic phenomena.*

the younger and the older patient for each of the types of thromboembolic hazards? To this query, Figure 98 gives a striking and obvious answer. *In comparisons with the control group, every major type of thromboembolic complication within each of the two major age groups showed substantially fewer complications.* In view of the comparability of the two groups, this achievement must be credited to anticoagulant therapy.

Finally, one can examine the details as they relate to the relative effectivness of anticoagulants with different types of thromboembolic phenomena. Differences in the age pattern under anticoagulants throw light on *this point. In contrast* to upward trends in the control group, extensions of myocardial infarctions were lower rather than higher in *the older age components* of the treated group and cerebral, peripheral, and visceral emboli showed little change with age. On

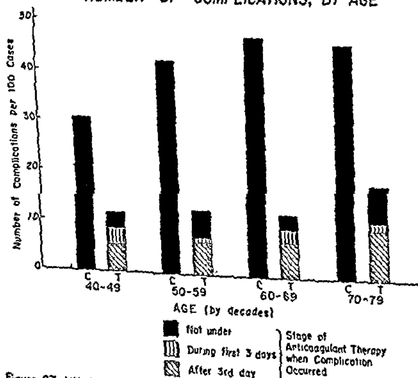


Figure 97. NUMBER OF COMPLICATIONS, BY AGE: Average number of thromboembolic complications per hundred cases occurring in control and treated groups, by age and status of anticoagulant therapy at time complication developed.

the other hand, venous thromboses increased rather than decreased with age and pulmonary emboli increased somewhat more with age than in the control group.

Unless these results are due to chance or nonrelevant factors, it follows inevitably from these alterations in the age pattern that (1) anticoagulant therapy was associated with more spectacular reductions in the incidence of secondary myocardial infarctions and cerebral, peripheral, and visceral emboli in older persons than in younger, and (2) reductions under anticoagulants in pulmonary emboli and venous thromboses were less conspicuous in older persons than with younger. These observations suggest that perhaps the previously mentioned contrast in the relative effectiveness of anticoagulants in preventing embolization from mural thrombi and in preventing venous thromboses increases with age.*

Sex Differences in Complications

Sex differences in thromboembolic complications constitute a second focus of probable medical interest around which data by patient-type may be organized. Table 101 and Figure 99 summarize the major rates relevant to sex differences. They have been standardized for age to eliminate irrelevant age differences insofar as feasible since otherwise the fact that women tend to develop coronary thrombosis with myocardial infarction at a later age than men would obscure and reduce sex differences in total rates. The basic counts and rates by sex for

* While the relatively poor record of anticoagulants with pulmonary emboli may seem contradictory to this pattern, the pulmonary infarctions may well have been due largely to embolization from venous thromboses in the legs rather than to embolization from mural thrombi on the right side of the heart. Unfortunately, however, due to the common custom in this country, autopsy studies of the veins of the legs were made in too few cases to confirm this point. At autopsy, the number of chambers showing mural thrombi was less on the

ter XIII). Among the 41 treated cases examined at autopsy, only 2 showed any mural thrombi on the right side of the heart.

TYPES OF COMPLICATIONS, BY AGE

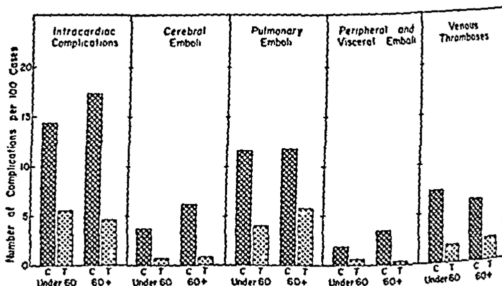


Figure 98. TYPES OF COMPLICATIONS, BY AGE: *Average number of thromboembolic complications of various types per hundred cases in control and treated groups among patients under sixty years of age and corresponding averages among patients of sixty years and over.*

specific ages are given in Appendix F, Table 44.

Three major conclusions are immediately apparent from these presentations: (1) *without anticoagulants, the risk of thromboembolic complications was greater in men than in women,* (2) *anticoagulant therapy was associated with very substantial reductions in the incidence of thromboembolic complications for both men and women,* and (3) *as a result of slightly greater reductions through anticoagulant therapy in the case of men, sex differences in the incidence of complications were all but eliminated in the treated group.*

TABLE 101

COMPLICATIONS, BY SEX. Percentage of Cases in the Control and Treated Groups Developing One or More Thromboembolic Complications and Average Number of Such Complications per Hundred Cases, by Sex

Sex and Treatment Group	Total Cases Observed	Thromboembolic Complication Rates Standardized for Age[a]	
		Percentage of Cases Developing One or More Thromboembolic Complications	Average Number of Thromboembolic Complications per 100 Cases
Control group			
Males	346	27 2	43 5[b]
Females	96	20.1	31 2[b]
Treated group			
Males	443	10.5	12 4
Females	146	9 4	12 0

[a] Standardization for age corrects for major differences in the age composition of each sex group by combining the actual rates for specific age and sex subgroups into weighted rates for all males and females in which each age component in the male group was given the same weight as the corresponding age component in the female group. The numbers of cases in each age group in the total sample were used as weights in these computations. Since the rates for specific age groups for females are based on small samples and are therefore subject to marked chance fluctuations, the age-standardized rates quoted must be considered approximate only

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B

Significance tests support the second of these conclusions since the difference between the control and treated groups in the average number of complications per hundred cases was found of borderline significance for females and highly significant for males. The first conclusion must, however, remain tentative since the differences between men and women within the treated group were too small to be statistically significant for samples of this size. Nevertheless, since in the control group males were found consistently higher than females in all major age groups in the average number of complications per hundred cases, the existence of sex differences in complications in the absence of anticoagulant therapy is perhaps real.

The comparison of each specific age and sex group rate for the treated group with its corresponding control group rate yields percentages which seem to support a further conclusion, namely, that anticoagulants become more effective in men but less effective in women as age increases. For men this conclusion may well be warranted but in the case of women, the sample sizes for the various age subgroups were too small to lend confidence to any such inference. Moreover, *the effects of anticoagulants were in any case so marked in practically all age and sex subgroups as to justify more than amply the giving to all persons regardless of age or sex the advantages of anticoagulant protection.*

Severity and Risk Classifications of Onset in Relation to Subsequent Thromboembolic Complications

Findings by Severity Classifications

A regrouping of the data by severity at onset serves to provide further clues for predicting the probability of complications and hence the need for anticoagulants. Data on complications in relation to the attending physician's estimate of the severity of the patient's illness at onset are given in Table 102 and in Figure 100. To eliminate insofar

the other hand, venous thromboses increased rather than decreased with age and pulmonary emboli increased somewhat more with age than in the control group.

Unless these results are due to chance or nonrelevant factors, it follows inevitably from these alterations in the age pattern that (1) anticoagulant therapy was associated with more spectacular reductions in the incidence of secondary myocardial infarctions and cerebral, peripheral, and visceral emboli in older persons than in younger, and (2) reductions under anticoagulants in pulmonary emboli and venous thromboses were less conspicuous in older persons than with younger. These observations suggest that perhaps the previously mentioned contrast in the relative effectiveness of anticoagulants in preventing embolization from mural thrombi and in preventing venous thromboses increases with age.*

* While the relatively poor record of anticoagulants with pulmonary emboli may seem contradictory to this pattern, the pulmonary infarctions may well have been due largely to embolization from venous thromboses in the legs rather than to embolization from mural thrombi on the right side of the heart. Unfortunately, however, due to the common custom in this country, autopsy studies of the veins of the legs were made in too few cases to confirm this point. At autopsy, the number of chambers showing mural thrombi was less on the right side of the heart than on the left and the reduction associated with anticoagulant therapy was also greater on the right side (see Table 159, Chapter XIII). Among the 41 treated cases examined at autopsy, only 2 showed any mural thrombi on the right side of the heart.

Sex Differences in Complications

Sex differences in thromboembolic complications constitute a second focus of probable medical interest around which data by patient-type may be organized. Table 101 and Figure 99 summarize the major rates relevant to sex differences. They have been standardized for age to eliminate irrelevant age differences insofar as feasible since otherwise the fact that women tend to develop coronary thrombosis with myocardial infarction at a later age than men would obscure and reduce sex differences in total rates. The basic counts and rates by sex for

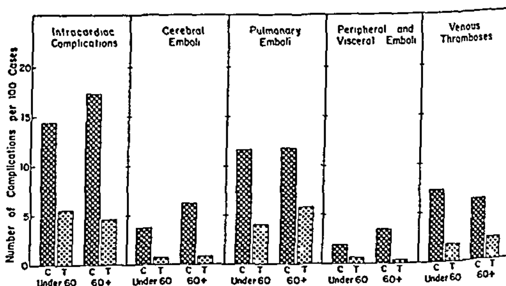


Figure 98. TYPES OF COMPLICATIONS, BY AGE: Average number of thromboembolic complications of various types per hundred cases in control and treated groups among patients under sixty years of age and corresponding averages among patients of sixty years and over.

nation for this relationship. Whatever the explanation, however, *there can be little doubt that patients who appear severely ill at onset have an especially urgent need for anticoagulant therapy.*

Is the physician therefore justified in concluding that anticoagulant therapy is needed *only* by patients severely ill at onset? A reinspection of Table 102 reveals further that even control group patients considered only mildly or moderately ill at onset had in this series a more than a one-in-five chance of developing complications without anticoagulants and that they averaged more than three complications for each ten patients. Since many of these complications were severely damaging to the patients, the *need for maximum available protection even for cases only mildly or moderately ill is evident.*

Further examination of Table 102 and Figure 100 give additional evidence that anticoagulants provided substantial protection regardless of the severity of the attack. Both those severely ill at onset and those mildly or moderately ill showed markedly lower rates in the treated group than in the control group, regardless of whether the rate under consideration was the percentage of cases developing complications or the number of complications developed per hundred cases. The contrasts on the latter basis were tested statistically and found to be "highly significant" for both severity levels. Among patients mildly or moderately ill at onset the treated group rate of complications per hundred cases was only 26 per cent of the "expected" or control group figure, while among patients severely ill at onset, the treated group rate was only 37 per cent of the "expected" rate. *Anticoagulants were thus clearly effective in both mild and severe cases.*

The slightly greater proportionate reductions achieved with cases mild or moderate at onset, apparent in the rates quoted, can also be observed in Figure 100. While the differences were small enough to leave doubt as

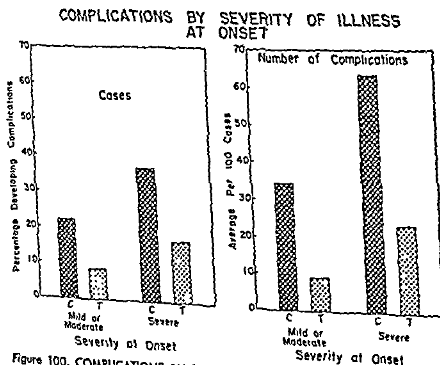


Figure 100. COMPLICATIONS BY SEVERITY OF ILLNESS AT ONSET: Percentage of cases in control and treated groups developing *one or more* thromboembolic complications and average number of such complications per hundred cases, by ... rity of illness at onset (rates standardized for age).

COMPLICATIONS, BY SEX

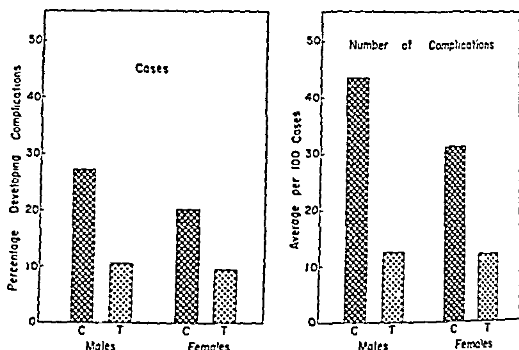


Figure 99. COMPLICATIONS, BY SEX: Percentage of cases in control and treated groups developing one or more thromboembolic complications and average number of such complications per hundred cases, by sex (rates standardized for age).

TABLE 102

COMPLICATIONS, BY SEVERITY OF ILLNESS AT ONSET: *Percentage of Cases in the Control and Treated Groups Developing One or More Thromboembolic Complications and Average Number of Such Complications per Hundred Cases, by Severity of Illness at Onset*

Severity at Onset and Treatment Group	Total Cases Observed	Thromboembolic Complication Rates Standardized for Age[a]: Percentage of Cases Developing One or More Thromboembolic Complications	Thromboembolic Complication Rates Standardized for Age[a]: Average Number of Thromboembolic Complications per 100 Cases
Control group:			
Cases severe at onset	116	36.8	63.3[b]
Cases mild or moderate at onset	326	22.0	34.2[b]
Treated group:			
Cases severe at onset	181	16.9	23.3
Cases mild or moderate at onset	408	8.5	9.0

[a] For explanation of process of standardization, see footnote a of Table 101.

[b] Corrected for exceptions in treatment. For [illegible] see Appendix B.

as feasible the influence of age factors irrelevant to the comparisons at issue, the rates have been standardized for age. The detailed counts appear in Appendix F, Table 45.

From Figure 100 it is clear that the physician's estimate of the severity of the case at onset has important predictive value. In the control group about half again as many of the cases considered severe at onset developed thromboembolic complications as did those mild or moderate at onset (36.8 per cent *vs.* 22.0 per cent). The severely ill group also showed nearly twice as many complications on the average as did the mild and moderate group (63 per 100 *vs.* 34 per 100). Contrasts in relation to severity at onset were even more marked in the treated group, but since these were influenced by anticoagulant therapy, they cannot be considered to represent an underlying biological pattern. In both the control and treated groups the differences in number of complications in relation to severity are statistically highly significant.

The data do not reveal the medical expla-

nation for this relationship. Whatever the explanation, however, *there can be little doubt that patients who appear severely ill at onset have an especially urgent need for anticoagulant therapy*

Is the physician therefore justified in concluding that anticoagulant therapy is needed *only* by patients severely ill at onset? A reinspection of Table 102 reveals further that even control group patients considered only mildly or moderately ill at onset had in this series a more than a one-in-five chance of developing complications without anticoagulants and that they averaged more than three complications for each ten patients. Since many of these complications were severely damaging to the patients, the *need for maximum available protection even for cases only mildly or moderately ill is evident.*

Further examination of Table 102 and Figure 100 give additional evidence that anticoagulants provided substantial protection regardless of the severity of the attack. Both those severely ill at onset and those mildly or moderately ill showed markedly lower rates in the treated group than in the control group, regardless of whether the rate under consideration was the percentage of cases developing complications or the number of complications developed per hundred cases. The contrasts on the latter basis were tested statistically and found to be "highly significant" for both severity levels. Among patients mildly or moderately ill at onset the treated group rate of complications per hundred cases was only 26 per cent of the "expected" or control group figure, while among patients severely ill at onset, the treated group rate was only 37 per cent of the "expected" rate. *Anticoagulants were thus clearly effective in both mild and severe cases.*

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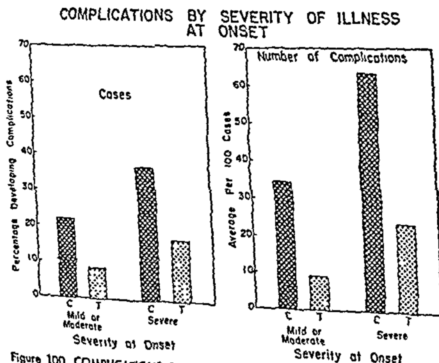


Figure 100. COMPLICATIONS BY SEVERITY OF ILLNESS AT ONSET: Percentage of cases in control and treated groups developing one or more thromboembolic complications and average number of such complications per hundred cases, by severity of illness at onset (rates standardized for age).

to their meaning and reliability, it appears that anticoagulant therapy was relatively slightly more effective with patients mildly or moderately ill at onset than with patients severely ill.[1] Whatever the meaning of this minor difference, *these findings do not support a clinical policy of confining anticoagulant therapy to patients appearing severely ill at onset.*

Findings by Risk Classifications

The foregoing data portray the findings for severity classifications based on the attending physician's general estimate of severity at onset. Except for the requirement that separate estimates be made for severity at onset and severity during the course of the illness, no attempt was made to outline for these physicians the basis on which they should classify severity. Subsequent to the completion of the field work for the present series, however, Russek et al.[209] have proposed that definite and somewhat complex criteria be used to screen myocardial infarction cases and that anticoagulants not be given to those who appear to be "good risk" cases by these criteria. These investigators have maintained that a satisfactory prediction of risk could be made from the facts available on the day of hospital admission, including medical history, and have proposed the following as poor risk indicators:

1. Previous myocardial infarction
2. Intractable pain
3. Extreme degree or persistence of shock
4. Significant enlargement of heart
5. Gallop rhythm
6. Congestive heart failure
7. Auricular fibrillation or flutter, intraventricular block
8. Ventricular tachycardia
9. Diabetic acidosis
10. Obesity
11. Previous history of
    - (a) Pulmonary embolism
    - (b) Varicosities in the lower extremities
    - (c) Thrombophlebitis (past or present)
12. Other states predisposing to thrombosis

It should be noted that the above list does not include arteriosclerosis, hypertension, or anginal syndrome and that "other states predisposing to thromboses" are not defined.

Russek and his co-workers have applied this definition in two series.[209] They have reported very low death and thromboembolic complication rates in good as compared with poor risk cases and from these findings have concluded that the risk of thromboembolism in good risk cases is so slight as not to justify the use of anticoagulant therapy. In order to test this proposal, the cases in the present series were also divided into good and poor risk groups by criteria designed to approximate those of Russek et al. within the limitations imposed by the data as reported and coded for other phases of the present analysis. Classification was based on the patient's known history and such characteristics of his illness as became apparent within one

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[1] It seemed possible that this apparent difference in effectiveness of anticoagulant therapy resulted from the fact that severe cases survived longer and in larger numbers in the treated group than in the control group, probably as a direct result of anticoagulant therapy and therefore had more days per case in which to develop complications. It was found, in fact, that severe cases in the treated group were observed for 2 6 days longer on the average than were severe cases in the control [illegible] the benefits of anticoagulant therapy would have shown up in a more favorable light. To eliminate the effect of this factor on comparisons, the rates were recomputed in terms of number of complications per thousand days observed. This refinement reduced the difference slightly but did not elim- [illegible] the new treated [illegible] (7.3) was [illegible] ate (23 5). For mild or moderately ill patients, the new treated group rate (2 2) was 25 per cent of the new control group rate (8.9).

k after onset.[a] The following were considered indicators of poor risk:

1. Previous myocardial infarction
2. Fourth degree pain, first week
3. Initial shock, fourth degree
4. Cardiac enlargement prior to onset
5. Gallop rhythm, first week
6. Initial congestive heart failure or congestive heart failure in history
7. Auricular fibrillation, auricular flutter, or any type of heart block, first week
8. Maximum pulse 110 or more, first week
9. [illegible]

(a) Pulmonary infarction or embolism
(b) Varicose veins in legs
(c) Thrombophlebitis
(d) Other thromboembolic phenomena

Other states predisposing to thrombosis
(a) Polycythemia, current
(b) Cancer, current
(c) Cerebral accident, aphasia, or hemiplegia when believed due to cerebral embolus, current or in previous history

By these criteria, 83 per cent of the cases the *present* series were found to be poor k cases as contrasted with 53 per cent in ussek's combined series Some of this difference is undoubtedly due to lack of full comparability in poor risk criteria used in the two series.[v] The extent of differences of this nature could not be tested partly because of the absence of definitions.[w] It does not seem probable, however, that differences in critieria and definition could have been sufficient to account for such a substantial difference as this. *Neither can the difference* be explained on the basis of differences in the severity of the series as a whole or by the inclusion of more mild or doubtful cases in Russek's series since the general mortality was higher for Russek's combined series than for the present control group.

One may assume, therefore, that the difference was created in part by a more rigorous application of the poor risk critiera in the present series, in part by more detailed attention to available records, in part by consideration of findings after the first day of hospitalization, and perhaps also in part by the availability of fuller basic records and case histories. The relation of these factors to the proportion of poor risk cases found is evident when it is recalled that a positive finding of at least one of the listed conditions was required before the case was considered a poor risk. Under the procedure recommended for screening, any vagueness in history taking, any lack of previous medi-

[a] Since cases in the present series were not hospitalised on the average until the third day after nset of the attack, and since the critical symptoms in question usually appear very soon after he attack, data based on the first week of the illess as here used should not give findings that liffer substantially from those based on information available to the physician on the day of hospital admission. In the present analysis, if hospitalization did not occur until after the first week, the original *records* were searched and classifications based on actual occurrences on or before the first day of hospitalization

[v] Some of this difference is due to the use in the present series of a maximum pulse of 110 or more instead of "ventricular tachycardia" in Russek's series Another difference involved the use of the first week instead of the day of admission (see footnote u) If persistent ventricular tachycardia had been considered a poor risk criterion in substitution for pulse rates of 110 or more, the percentage of poor risk cases would have been reduced from 83 per cent to 77 per cent. Even this figure is still substantially above Russek's 53 per cent Probably unfavorable changes in the patient's status between the end of the first day of hospitalization and the end of the first week of hospitalization are a more important factor in the high proportion of poor risk cases found in the present study.

[w] This is illustrated by the absence of published definitions for Russek's criteria of "intractable pain" and "significant enlargement of the heart."

to their meaning and reliability, it appears that anticoagulant therapy was relatively slightly more effective with patients mildly or moderately ill at onset than with patients severely ill.[t] Whatever the meaning of this minor difference, *these findings do not support a clinical policy of confining anticoagulant therapy to patients appearing severely ill at onset.*

Findings by Risk Classifications

The foregoing data portray the findings for severity classifications based on the attending physician's general estimate of severity at onset. Except for the requirement that separate estimates be made for severity at onset and severity during the course of the illness, no attempt was made to outline for these physicians the basis on which they should classify severity. Subsequent to the completion of the field work for the present series, however, Russek et al.[44] have proposed that definite and somewhat complex criteria be used to screen myocardial infarction cases and that anticoagulants not be given to those who appear to be "good risk" cases by these criteria. These investigators have maintained that a satisfactory prediction of risk could be made from the facts available on the day of hospital admission, including medical history, and have proposed the following as poor risk indicators:

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10. Obesity
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    (a) Pulmonary embolism
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    (c) Thrombophlebitis (past or present)
12. Other states predisposing to thrombosis

It should be noted that the above list does not include arteriosclerosis, hypertension, or anginal syndrome and that "other states predisposing to thromboses" are not defined.

Russek and his co-workers have applied this definition in two series.[44] They have reported very low death and thromboembolic complication rates in good as compared with poor risk cases and from these findings have concluded that the risk of thromboembolism in good risk cases is so slight as not to justify the use of anticoagulant therapy. In order to test this proposal, the cases in the present series were also divided into good and poor risk groups by criteria designed to approximate those of Russek et al. within the limitations imposed by the data as reported and coded for other phases of the present analysis. Classification was based on the patient's known history and such characteristics of his illness as became apparent within one

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[t] It seemed possible that this apparent difference in effectiveness of anticoagulant therapy resulted from the fact that severe cases survived longer and in larger numbers in the treated group than in the control group, probably as a direct result of anticoagulant therapy and therefore had more days per case in which to develop complications. It was found, in fact, that severe cases in the treated group were observed for 9.6 days longer on the average than were severe cases in the control group. If the control group had been observed for these additional days, it would undoubtedly have shown a higher complication rate and as a result the benefits of anticoagulant therapy would have [illegible] To eliminate [illegible] sons, the rates [illegible] r of complica- [illegible] treatment [illegible] ot elim- [illegible] treated group rate per thousand days observed (7.3) was 31 per cent of the new control group rate (23.5). For mild or moderately ill patients, the new treated group rate (8.6) was 95 per cent of the new control group rate (9.0).

week after onset.[u] The following were considered indicators of poor risk:

1. Previous myocardial infarction
2. Fourth degree pain, first week
3. Initial shock, fourth degree
4. Cardiac enlargement prior to onset
5. Gallop rhythm, first week
6. Initial congestive heart failure or congestive heart failure in history
7. Auricular fibrillation, auricular flutter, or any type of heart block, first week
8. Maximum pulse 110 or more, first week
9. Diabetes during the illness
10. Overweight 30 per cent or more
11. Previous history of
    (a) Pulmonary infarction or embolism
    (b) Varicose veins in legs
    (c) Thrombophlebitis
    (d) Other thromboembolic phenomena
12. Other states predisposing to thrombosis
    (a) Polycythemia, current
    (b) Cancer, current
    (c) Cerebral accident, aphasia, or hemiplegia when believed due to cerebral embolus, current or in previous history

By these criteria, 83 per cent of the cases in the present series were found to be *poor risk* cases as contrasted with 53 per cent in Russek's combined series. Some of this difference is undoubtedly due to lack of full comparability in poor risk criteria used in the two series.[v] The extent of differences of this nature could not be tested partly because of the absence of definitions.[w] It does not seem probable, however, that differences in critieria and definition could have been sufficient to account for such a substantial difference as this. Neither can the difference be explained on the basis of differences in the severity of the series as a whole or by the inclusion of more mild or doubtful cases in Russek's series since the general mortality was higher for Russek's combined series than for the present control group.

One may [illegible]

present series, in part by more detailed attention to available records, in part by consideration of findings after the first day of hospitalization, and perhaps also in part by the availability of fuller basic records and case histories. The relation of these factors to the proportion of poor risk cases found is *evident* when it is recalled that a positive finding of at least one of the listed conditions was required before the case was considered a poor risk. Under the procedure recommended for screening, any vagueness in history taking, any lack of previous medi-

[u] Since cases in the present series were not hospitalized on the average until the third day after onset of the attack, and since the critical symptoms in question usually appear very soon after the attack, data based on the first week of the illness as here used should not give findings that differ substantially from those based on information available to the physician on the day of hospital admission. In the present analysis, if hospitalization did not occur until after the first week, the original records were searched and classifications based on actual *occurrences* on or before the first day of hospitalization.

[v] Some of this difference is due to the use in the present series of a maximum pulse of 110 or more instead of "ventricular tachycardia" in Russek's series. Another difference involved the use of the first week instead of the day of admission (see footnote u). *If persistent ventricular tachycardia* had been considered a poor risk criterion in substitution *for* pulse rates of 110 or more, the percentage of poor risk cases would have been reduced from 83 per cent to 77 per cent. Even this figure is still substantially *above Russek's 53* per cent. *Probably* unfavorable changes in the patient's status between the end of the first day of hospitalization and the end of the first week of hospitalization are a more important *factor* in the high proportion of poor risk cases found in the present study.

[w] This is illustrated by the absence of published definitions for Russek's criteria of "intractable pain" and "significant enlargement of the heart."

cal diagnostic service, any omissions in hospital records, or any oversights in the process of record review potentially can prevent the recognition of a case as a poor risk. The ease with which poor risk indicators could be overlooked was, in fact, abundantly illustrated in the course of the preparation of the present tabulations. *These experiences brought the staff to a keen awareness of the degree of risk involved for the patient and the heavy responsibility for thoroughness placed on the admitting physician in any system under which patients are not given anticoagulant protection unless they are found to have shown, on or before the day of hospital admission, some positive poor risk indication.*

Counts of thromboembolic complications for the good and poor risk cases yielded the results for thromboembolic complications shown in Table 103 and Figure 101. Details appear in Appendix F, Table 46. Corresponding data for deaths are reported in Chapter XI and for hemorrhages, in Chapter IX.

In general, the findings confirm those previously presented for severity classifications. *Good risk cases showed fewer complications than poor risk cases both in terms of the percentage of cases developing complications and in terms of the average number of complications per hundred cases. Anticoagulant therapy is thus especially needed by poor risk cases. Substantial improvements through anticoagu-*

TABLE 103

COMPLICATIONS IN GOOD AND POOR RISK CASES: Percentage of Cases Developing One or More Thromboembolic Complications and Number of Complications of Various Types per Hundred Cases in the Control and Treated Groups among Patients Estimated to Have Been Good and Poor Risk Cases by Criteria Approximating Those of Russek *et al.*[111]

Estimate of Risk	Total Cases Observed		Percentage of Cases Developing One or More Thromboembolic Complications		Average Number of Thromboembolic Complications per 100 Cases: All Types		Intracardiac Complications		Emboli[b, c]		Venous Thromboses	
	Control Group	Treated Group	Control Group	Treated Group	Control Group[a]	Treated Group	Control Group[a]	Treated Group	Control Group[a]	Treated Group	Control Group[a]	Treated Group
Moderately strict definition of good risk:[d]												
Good risk cases	65	114	23.1	8.8	28.6	8.8	15.9	7.9	9.5	—	3 2	.9
Poor risk cases	377	475	26 5	11.4	44 1	14.1	15.8	4.4	20.9	7.4	7.4	2 3
Very strict definition of good risk:[e]												
Good risk cases	24	47	*20.8*	10 6	*34.6*	10 6	*8.7*	10.6	*21.7*	—	*4.2*	—
Poor risk cases	418	542	26.3	10.9	42.2	13.3	16.2	4.6	19.1	6.5	6.9	2 2

Note: *Italics are used when percentages and rates quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[b] The percentage of cases developing emboli in the control group for the good and poor risk categories in sequence were: 7.7 and 14.6 for the moderately strict definition and *16.7* and 13 4, for the very strict definition. Corresponding percentages for the treated group were: 0 0 and 6.3; 0.0 and 5 5 One control group case in the poor risk category developing an arterial thrombosis has been excluded from the foregoing counts.

[c] In one treated group and two control group cases in the poor risk category and in one control group case with 3 degrees of pain the only unfavorable factor, it was uncertain whether the complication was an embolus or thrombus.

[d] See definition on p. 231.

[e] Same definition as for moderately strict except that third degree pain was added to the criteria for poor risk.

lant therapy were likewise apparent for both good and poor risk cases. In spite of the rigorous selection used in segregating good risk cases, complication rates for this group were little improved over those for the much larger group previously designated as mild or moderate at onset

In this tabulation particular interest centered, of course, on the complication record for good risk cases. When thus rigorously defined, did such cases, in fact, show so few complications that anticoagulant therapy would not be warranted? Even though the criteria for good risk were so strict that only 65 control group cases could qualify, 15 of these 65 (23.1 per cent) developed a total of 18 complications (10 intracardiac complications, 6 emboli, and 2 venous thromboses). Complications were also evident in the good risk component of the treated group. Of the 114 treated group good risk cases, 10 (8.8 per cent) developed a total of 10 complications One of these was a venous thrombosis and the other 9 were intracardiac in location. All except one occurred either at times when anticoagulants were not in use or when prothrombin times were below the therapeutic range.* Even with these small samples, the difference associated with anticoagulant therapy for good risk cases is of borderline significance statistically.

Experience with two control group cases that, according to Russek's criteria were

* In two instances the prothrombin time could not be classified since no prothrombin time was reported for the day the complications developed.

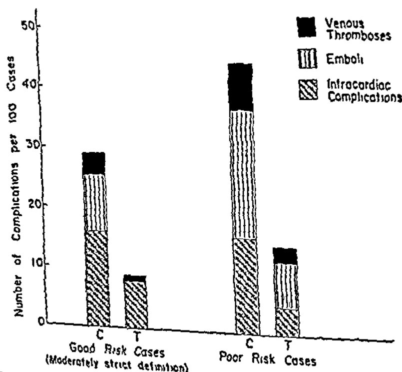


Figure 101. COMPLICATIONS IN GOOD AND POOR RISK CASES: Average number of thromboembolic complications of various types developing per hundred cases in the control and treated groups among patients estimated to have been good and poor risk cases by criteria approximating those of Russek et al.[209]

cal diagnostic service, any omissions in hospital records, or any oversights in the process of record review potentially can prevent the recognition of a case as a poor risk. The ease with which poor risk indicators could be overlooked was, in fact, abundantly illustrated in the course of the preparation of the present tabulations. *These experiences brought the staff to a keen awareness of the degree of risk involved for the patient and the heavy responsibility for thoroughness placed on the admitting physician in any system under which patients are not given anticoagulant protection unless they are found to have shown, on or before the day of hospital admission, some positive poor risk indication.*

Counts of thromboembolic complications for the good and poor risk cases yielded the results for thromboembolic complications shown in Table 103 and Figure 101. Details appear in Appendix F, Table 46. Corresponding data for deaths are reported in Chapter XI and for hemorrhages, in Chapter IX.

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TABLE 103

COMPLICATIONS IN GOOD AND POOR RISK CASES: Percentage of Cases Developing One or More Thromboembolic Complications and Number of Complications of Various Types per Hundred Cases in the Control and Treated Groups among Patients Estimated to Have Been Good and Poor Risk Cases by Criteria Approximating Those of Russek *et al.*[201]

Estimate of Risk	Total Cases Observed		Percentage of Cases Developing One or More Thromboembolic Complications		Average Number of Thromboembolic Complications per 100 Cases							
					All Types		Intracardiac Complications		Emboli[b, c]		Venous Thromboses	
	Control Group	Treated Group	Control Group	Treated Group	Control Group[a]	Treated Group	Control Group[a]	Treated Group	Control Group[a]	Treated Group	Control Group[a]	Treated Group
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Note: *Italics are used when percentages and rates quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[b] The percentage of cases developing emboli in the control group for the good and poor risk cate- [illegible] for the very [illegible] d 5 5. One [illegible] uded from the foregoing counts.

[c] In one treated group and two control group cases in the poor risk category and in one control group case with 3 degrees of pain the only unfavorable factor, it was uncertain whether the complication was an embolus or thrombus.

[d] See definition on p. 231.

[e] Same definition as for moderately strict except that third degree pain was added to the criteria for poor risk.

difference remains even when no question of risk definition is involved. Could it be then that the patients in Russek's series were less severely ill than those in the present series and therefore showed a lower complication rate? This interpretation is in turn contradicted by the fact that 33.4 per cent of the patients in Russek's combined series died while only 23.4 per cent of all control group patients in the present series died. Still another explanation might be surmised, namely, overdiagnoses of thromboembolic phenomena in the present study. The autopsy analysis refutes this theory since it demonstrates that underdiagnosis rather than overdiagnosis of thromboembolic phenomena was typical of the present series. Moreover, underdiagnosis occurred more frequently in the control than in the treated group.

The exclusion of these four explanations leads to the conclusion that the difference probably lies to an important degree in differences in the completeness of diagnosis and recording of thromboembolic phenomena.[bb] In the present series it was possible to record direct observations of patients *after* the phenomena to be observed had been defined for study purposes and to improve both observation and recording through correspondence and direct contact with the attending staff. In Russek's two series, on the other hand, the counts were necessarily obtained by a review of past hospital records in which recordings were made with no knowledge of the research functions for which they would be used. Omissions in recording and underdiagnosis of thromboembolic complications are inevitable under such circumstances and may have been sufficient in this case to explain the difference in the findings reported.

On the basis of this review, therefore, the present authors reaffirm their position that when laboratory and other circumstances are such as to make anticoagulant therapy feasible, such therapy should not be limited to poor risk cases only. In support of this position, it has been shown that (1) good risk cases not receiving anticoagulants showed a substantial number of thromboembolic complications, (2) good risk cases showed an improved thromboembolic record when given anticoagulant therapy, (3) serious bleeding due to anticoagulants was very infrequent (see Chapter IX), and (4) dependence upon screening for good risk cases involves a great possibility of error.

Weight in Relation to Complications

There is some evidence to indicate that thromboembolic complications are more apt to occur in the obese than in patients with normal or slightly substandard weights. Both Snell[171] and Ochsner[148] have reported a higher incidence of pulmonary embolism among obese postoperative patients than among such patients whose weights are normal, irrespective of the surgical condition for which an operation was performed.

It has been suggested that the predisposition to thromboembolism among the obese is related to hyperlipemia, or to hypercholesterolemia, rather than to obesity per se. Pohle and Stewart[155] observed that grossly lipemic plasma tended to have a shortened prothrombin time. When tested following meals which were heavy in fat, plasma prothrombin times were accelerated. However, Martin, Curfman and Cavano[113] were unable to demonstrate any difference in prothrombin times determined post-prandially and Overman, Newman and Wright[170] have shown that a high cholesterol diet ingested for periods of one month or more had no effect on the prothrombin time of normal subjects. Interest in the relation of hyperlipemia and of hypercholesterolemia to blood coagulation has been aroused by recent research on the influence of heparin on these phenomena.

One must conclude at the present time that there is no clear evidence as to the rela-

[bb] Since the published reports of the series of Russek et al do not list the types of thromboembolic phenomena included in their counts, it is possible that part of the difference is due to a difference in definition

"good risks" at the time of admission, will serve to illustrate how thromboembolic complications sometimes occur unexpectedly in exceedingly mild cases. The first case, a 56-year old man, admitted to the hospital because of an embolus in the right axillary artery, presented no history or signs or symptoms indicating a coronary attack and no evidence of previous coronary disease. An electrocardiogram revealed, however, a recent anteroseptal infarction. As an emergency measure he was given heparin for one day and an embolectomy was performed. Two days later he developed a pulmonary embolus and was again placed on heparin (as an exception) for five days. Thus, even with this temporary anticoagulant protection, this "good risk" case with a completely "silent" coronary thrombosis developed two thromboembolic complications within two weeks of the estimated date of onset. The second case, a 66-year old woman with an anterior infarction, was admitted to the hospital on an even day and received no anticoagulants. This patient developed an extension of her original myocardial infarction on the seventh day of her illness and a pulmonary embolus, on the ninth day. Tenderness of the right calf muscles on the 20th day and lasting 3 days was considered evidence for a probable thrombophlebitis. In this patient, therefore, we have an example of a so-called "good risk" case who developed *no less than three thromboembolic complications* during the course of her hospital stay. Additional cases of a similar nature could be cited.

Since some doubt existed as to whether third degree pain should or should not be considered equivalent to "intractable" pain as used in Russek's series,[y] the analysis was further extended by reducing still more the cases considered good risks in the present series by defining third degree pain in the first week as a poor risk indicator.[*] This procedure reduced the good risk groups to excessively small samples—24 cases in the control group and 47 cases in the treated group. The strictness of the criteria for good risk utilized in this second sifting is illustrated by the fact that its application eliminated all deaths from both the control and treated group good risk cases.[**] Nevertheless, even with this very restricting definition, 5 cases among the 24 good risk cases in the control group developed a total of 8 thromboembolic complications (2 intracardiac complications, 5 emboli, and 1 venous thrombosis) while 5 cases among the 47 good risk cases in the treated group developed 5 complications, all intracardiac in location. The revised definition does not alter the general conclusion. About a fifth of the good risk control group still showed thromboembolic complications.

In contrast to the fact that in this series more than 20 per cent of the control group good risk cases developed complications, Russek et al. have reported that in their combined series less than one per cent of the good risk cases showed thromboembolic complications without anticoagulant therapy. The difference is so marked that it can hardly be attributed to chance. How then can it be explained? It is clearly not merely a matter of the definition of good and poor risk cases since only 6 per cent of Russek's combined series, regardless of risk, showed thromboembolic complications as contrasted with 26 per cent of the total control group who developed thromboembolic complications in the present series. Thus a large

[y] The report form did not include data on whether it had proved possible to control the pain with narcotics.

[*] Other criteria for good and poor risk could also ... tempera- ... first ... on of good risk. When this criterion was actually tried, it was found once again that a presumably good risk group with surprising frequency developed thromboembolic complications. Forty-three per cent of the control group but only 18 per cent of the treated group with a low temperature record during the first week developed one or more thromboembolic complications within six weeks of onset.

[**] For data on deaths among good and poor risk cases, see Chapter XI

is consistent with that from studies of postoperative embolism and thrombosis, which have also shown that these sequelae are significantly more frequent in overweight persons[4,21] From this combined evidence, it seems reasonable to conclude that *overweight is also associated with excessive thromboembolic complications following myocardial infarction.*

In contrast to overweight, underweight showed little clear relation to thromboembolic complications. Of four possible comparisons in Table 104 between underweight and normal weight, three showed a better record for underweight persons than for persons of normal weight while in the fourth the relationship was reversed. Moreover, in each instance, the differences were small and not statistically significant. *Evidence from this study is therefore insufficient to support a deduction that, in comparison with normal weight, underweight status lowers the prospect that complications will develop.*

A comparison of the treated group rates with their corresponding control or "expected" rates yields contrasts remarkably favorable to anticoagulants in all three weight classifications. In each case these contrasts are readily apparent in Figure 102. Except for the case rate comparison for overweight persons,** differences of the observed amounts could be expected to occur on a chance basis less than one or twice in a hundred samples. *Anticoagulants apparently improved the complication record for persons at all weight levels.*

The evidence suggests further that *anticoagulants were somewhat more effective with patients of normal or subnormal weight than with obese patients.* On both types of rates

of these instances, correction for exceptions in treatment might have changed the significance classification.

** Comparison of the average number of com- [illegible] the control and treated groups in respect to the percentage of overweight cases developing complications yielded a probability slightly higher than 10 per cent that the difference after standardization could have occurred on a chance basis.

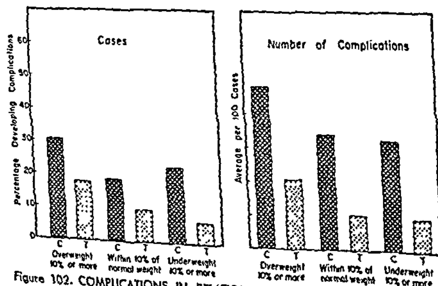


Figure 102. COMPLICATIONS IN RELATION TO WEIGHT STATUS: Percentage of cases in control and treated groups developing one or more thromboembolic complications and average number of such complications per hundred cases, by weight status in relation to normal (rates standardized for age).

tion between hyperlipemia and any increased tendency to intravascular clotting. Certainly it is not evident that the predisposition of the obese to thromboembolism is a result of any consistent hyperlipemia or hypercholesterolemia in these patients.

In view of the extent of interest in this issue, the experience of the present study was reviewed to ascertain what association, if any, existed between obesity and thromboembolic complications. The major findings in this regard appear in Table 104 and Figure 102. To increase comparability, the rates have been standardized for age. Details for specific age groups appear in Appendix F, Table 47.

Classification of weight (see explanation on page 31) followed the standards of the Metropolitan Life Insurance Company. For purposes of brevity, patients 10 per cent or more overweight are referred to in the present comment as obese; those 10 per cent or more below standard, as underweight; and those within 10 per cent of standard weight, as normal in weight. Unfortunately about a third of the sample could not be classified with respect to weight status because of the absence of information as to the patient's height, weight, or age. A review of the thromboembolic complication record indicates that the contrast between the control and treated groups would have been greater if these omissions had not been necessary.[cc]

As in other studies, thromboembolic phenomena were more frequent in obese patients than in those of normal weight. In the control group, the percentage of cases developing thromboembolic complications was 62 per cent higher among obese patients than among those of normal weight and in the treated group, 86 per cent higher. The number of complications per hundred patients was 41 per cent higher among the obese than among the normal in the control group and in the treated group, 98 per cent higher. In spite of the relatively small samples involved, this latter difference was sufficiently large to be highly significant statistically. The other differences were also substantial but, probably because of the small samples involved, they could not be demonstrated to be statistically significant.[dd] This evidence

TABLE 104

COMPLICATIONS IN RELATION TO WEIGHT STATUS: Percentage of Cases in the Control and Treated Groups Developing One or More Thromboembolic Complications and Average Number of Such Complications per Hundred Cases, by Weight Status in Relation to Normal

Weight Status in Relation to Normal and Treatment Group	Total Cases Observed[a]	Thromboembolic Complication Rates, Standardized for Age[b]	
		Percentage of Cases Developing One or More Thromboembolic Complications	Average Number of Thromboembolic Complications per 100 Cases
Control group:			
10% or more overweight	68	30.5	48.0[c]
Within 10% of normal weight	164	18.8	34.0[c]
10% or more underweight	61	22.9	32.4[c]
Treated group:			
10% or more overweight	90	17.9	20.8
Within 10% of normal weight	239	9.6	10.5
10% or more underweight	84	6.4	9.6

[a] Because of lack of a report of height or weight or age, the weight status of 149 control group cases and 176 treated group cases could not be computed. Complication rates for these cases of unknown weight appear in Appendix F Table 47.

[b] For explanation of process of standardization, see footnote a, Table 101.

[c] Data corrected for exceptions in treatment. For method of correction, see Appendix B.

[cc] This inference is derived from the fact that persons of unknown weight in the control group showed a complication rate similar to patients 10 per cent or more overweight, while persons of unknown weight in the treated group showed a complication rate considerably below the treated group rate for overweight persons.

[dd] Tests as usual were applied to rates before corrections for exceptions in treatment. In some

enced in any way the outcome of the basic anticoagulant experiment.

The general findings on complications by type of hospital service are summarized in Table 105 and Figure 103. Rates for the 31 cases receiving more than one type of care at different times during the period of observation are omitted because of their small number and intermediate status. The details by specific age groups for each type of service appearing in Appendix F Table 48 constitute the basis for the standardized rates used in *the textual discussion.*

In both the control and treated groups the private and semiprivate complication rates were below those for ward cases, but the differences were exceedingly slight and hardly visible in Figure 103. About one more ward than *private* patient among every two hundred in the control group and about two more ward than private patients per hundred in the treated group developed complications during the period of observation. The differences are not statistically significant. Similarly small differences prevailed in the case of the average number of complications per 100 cases, the differences by type of service being less than two complications per 100 cases in both treatment groups.

Since ward patients showed a higher death rate than private and semiprivate patients and were therefore observed for fewer days per case on the average, it seemed possible that the lack of difference was due to the type of rate used. However, a restatement of the findings in terms of the number of complications per thousand days observed (a basis that eliminates this extraneous influence) failed likewise to reveal differences of consequence. For the control group the ward rate was exactly the same as the private and semiprivate rate, namely, 12.0 complications per thousand days observed. The treated group rate for ward patients (3.9) was slightly above the private and semiprivate complication rate (3.2) but *the difference* was too slight to support without further evidence a deduction that the incidence of complications differs by type of hospital service received.

Several explanations for this lack of difference by type of care are plausible. Perhaps thromboembolic complications actually do not vary significantly by type of service or by the differing economic levels that these types of care reflect. There is certainly no obvious medical reason why they would be expected to vary in this manner. On the other hand, perhaps a lower basic rate for those of more fortunate economic status was

TABLE 105

COMPLICATIONS, BY TYPE OF SERVICE: Percentage of Cases in the Control and Treated Groups Developing One or More Thromboembolic Complications and Average Number of Such Complications per Hundred Cases among Patients Receiving *Private or Semiprivate* Care and among Patients Receiving Ward Care

Type of Service[a]	Total Cases Observed		Percentage of Cases Developing One or More Thromboembolic Complications (Rates Standardized for Age)[b]		Average Number of Thromboembolic Complications per 100 Cases	
	Control Group	Treated Group	Control Group	Treated Group	Control Group[c]	Treated Group
Private or semiprivate	155	221	25.6	10.0	43.0[d]	12.2[d]
Ward	281	343	26.4	11.8	41.7[e]	14.0[e]

[a] Tabulation omits 31 cases who received both ward and private or semiprivate care at different times during the period of observation.
[b] For explanation of process of standardization [illegible]
[c] Data are corre[illegible]
[d] Complications [illegible]
[e] Complications [illegible]

shown in Table 101 and in Figure 102, the reduction achieved with anticoagulants (i.e., the treated group rate stated as a percentage of the control group rate) was less with the overweight group than with the normal and underweight groups. The ranking of the relative probabilities that the differences were due to chance was also consistent with the inference that anticoagulants were less effective with overweight than with normal weight persons.[rr]

From the present study it is not possible to explain completely this apparent difference in effectiveness. To some extent the lower effectiveness is more apparent than real since it resulted in part from the great savings in deaths found associated with anticoagulant therapy among overweight persons (see Chapter XI), for, by the mere fact of improved survival rate, overweight patients in the treated group had more days of observation on which to develop complications. When this extraneous influence is eliminated by the use of day rates, the differences between the apparent effectiveness of anticoagulant therapy with overweight and normal persons is greatly reduced.[ss] Perhaps the remaining difference, if not due to chance, is related to the lower degree of prothrombin time responsiveness to dicumarol found characteristic of overweight persons in this study (see Chapter XII).

While the rates for specific age groups tempt one to speculate further as to the role of weight in intravascular clotting, most of the rates for specific age groups appearing in Appendix F Table 47 are based on too few cases for valid deductions. Observations are therefore limited to several of their more striking features. In this table it will be noted, for example, that the control group rates for obese patients 50 to 59 and 60 to 69 years of age were excessively high—64 complications per hundred cases on the average for the combined groups. This very high rate for obese control patients in the sixth and seventh decade suggests that perhaps obesity in the age range from 50 to 70 is a particularly important factor in intravascular clotting of all types. If this is actually the case, *obese patients in the middle age ranges are in particular need of anticoagulants.*

A second noteworthy feature of Appendix F, Table 47 is the substantial increase in complication rates for persons of normal weight in the eighth decade in both the control and treated groups. This increase in intravascular clotting is consistent with the general age trends previously discussed and may be related to the greater degree and longer duration of debilitation common among persons of this age.

Type of Hospital Service in Relation to Complications

Another possible relationship explored statistically was that between thromboembolic complications and the type of hospital service used in treating patients. It was anticipated that possibly economic status as reflected in eligibility for ward care might show some relation to complication rates, or that differences in care in observation or therapy under ward and private conditions might be reflected in complication rates. Since 65 per cent of the control group patients received ward care only, as compared with 59 per cent of the treated group, a check for such hidden influences was also needed in order to ascertain whether this minor departure from comparability influ

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[rr] In other words, the chances that the differences were due to chance were greater for the overweight group than for the normal weight group for both types of rates.

[ss] The number of complications per thousand days observed among obese patients in the treated group (5 4) was 37 per cent of the number of complications per thousand days in the control group (14 5). Among normal or underweight patients, the number of complications per thousand days observed in the treated group (2 9) was 32 per cent of the number of complications per thousand days in the control group (9.2). These percentages of "expected" are to be compared with the following

Complications in Relation to Location of the Original Infarction

In the effort to uncover other practical methods of predicting the probability of thromboembolic complications, the question was raised as to whether the site of the original infarction might influence in some way the probability of thromboembolic complications. To find the answer, cases exhibiting one or more thromboembolic complications were first separated into three groups according to the location of the original myocardial infarction and then the complications occurring in each group analyzed. *Anterior infarctions* included all infarctions reported as anterior, anterolateral, or anteroseptal. *Posterior infarctions* included all infarctions reported as posterior, posterolateral, or posteroseptal. The third group, *all other types*, was a miscellaneous one which for the control and treated groups combined included 15 cases with "septal" infarctions, 50 with a picture of "diffuse changes," 25 with "obscure sites," and 9 with "multiple infarctions."

The number of thromboembolic complications developing in patients whose original infarctions were anterior, posterior, or other types is given in Table 106 and Figure 104. The component sections of the bars help the reader to visualize the location of the complications that make up the totals. The actual counts and rates for each location are given in Appendix F, Table 49.

The findings do not suggest that the location of the infarction is of any real importance in complication rates. When the original infarction was posterior in location, the average number of complications per hundred cases was slightly but not strikingly higher than that when the original infarction was anterior (by 13 per cent in the control group and 8 per cent in the treated). These differences were not statistically significant for samples of this size. Moreover, when the rates were restated in terms of number per thousand days observed, they differed even less since patients with anterior infarctions showed a higher death rate than patients with posterior infarctions and therefore had less time in which to develop complications.

Rates for the various [illegible] Table 49). The differences in the totals in the case of the control group were almost entirely the result of more venous thromboses and pulmonary emboli in cases having posterior infarctions initially.

The category, all other types, presents more conspicuous contrasts with the other locations than did anterior and posterior, but the directions of the differences were not consistent in the control and treated groups. In view of the mixed character of this third group, its small numbers, and its high death rate (see Chapter XI), any possible conclusions as to the relation of these miscellaneous locations to the complication rate would have little application beyond the particular group involved.

TABLE 106

COMPLICATIONS, BY LOCATION OF ORIGINAL INFARCTION Average Number of Thromboembolic Complications per Hundred Cases in the Control and Treated Groups, by Location of Original Infarction

Location of Original Infarction	Total Cases Observed		Average Number of Thromboembolic Complications per 100 Cases	
	Control Group	Treated Group	Control Group[a]	Treated Group
Anterior infarction[b]	231	319	40.5	11.9
Posterior infarction[c]	171	211	45 9	12 8
All other types[d]	40	59	32 3	20 4

[a] Data are corrected for exceptions in treatment For method of correction, see Appendix B.

[b] Includes anterior, anterolateral, and anteroseptal infarctions

[c] Includes posterior, posterolateral, and posteroseptal infarctions

[d] Includes septal infarctions, infarctions characterized by diffuse changes, and infarctions whose site is obscure or unknown, and multiple infarctions at onset

obscured in the present study by more frequent recognition of existing thromboembolic developments under private and semiprivate types of service.

It is not possible from present evidence to ascertain which of these two possible explanations is the true one. It can only be said that *the observed differences in the present study were too slight to support a conclusion that low income persons are more subject to thromboembolic developments than those financially more fortunate. Neither do they support the conclusion that, in this study, ward patients were treated less energetically than private or semiprivate patients in respect to the essentials of anticoagulant therapy.*

When the control group rates are compared with those for the treated group within each type of service group, the comparisons differ little from those for the total control and treated groups which have already been discussed (see pages 195–196). In the present form, however, they can also be used to demonstrate the extent to which the somewhat higher proportion of ward cases in the control group actually influenced the central findings reported on pages 195–196 with respect to complications. When the percentages for cases developing one or more complications in the control and treated groups were standardized both for age and for the proportion of ward cases, the revised rates became: control group, 25.9 (instead of 26.0) per cent and treated group, 11.0 (instead of 10.9) per cent. *The changes with these corrections are inconsequential and do not alter the basic conclusion that the differences associated with anticoagulant therapy were highly significant statistically.*

COMPLICATIONS BY TYPE OF SERVICE

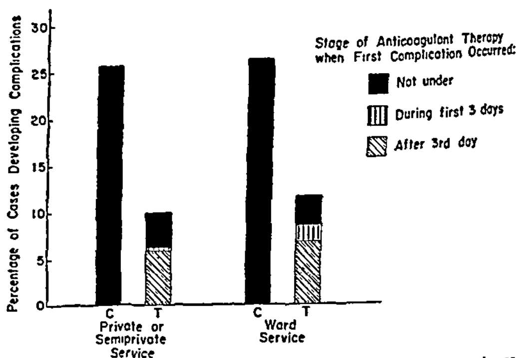


Figure 103. COMPLICATIONS BY TYPE OF SERVICE: Percentage of cases in control and treated groups developing one or more thromboembolic complications among patients receiving private or semiprivate service and among patients receiving ward service, by status of anticoagulant therapy at time of first complication (rates standardized for age).

Complications in Relation to Location of the Original Infarction

In the effort to uncover other practical methods of predicting the probability of thromboembolic complications, the question was raised as to whether the site of the original infarction might influence in some way the probability of thromboembolic complications. To find the answer, cases exhibiting one or more thromboembolic

plications occurring in each group analyzed. *Anterior infarctions* included all infarctions reported as anterior, anterolateral, or anteroseptal. *Posterior infarctions* included all infarctions reported as posterior, posterolateral, or posteroseptal. The third group, *all other types*, was a miscellaneous one which for the control and treated groups combined included 15 cases with "septal" infarctions, 50 with a picture of "diffuse changes," 25

TABLE 106

COMPLICATIONS, BY LOCATION OF ORIGINAL *INFARCTION*. Average Number of Thromboembolic Complications per Hundred Cases in the Control and Treated Groups, by Location of Original Infarction

Location of Original Infarction	Total Cases Observed		Average Number of Thromboembolic Complications per 100 Cases	
	Control Group	Treated Group	Control Group[a]	Treated Group
Anterior infarction[b]	231	319	40.5	11.9
Posterior infarction[c]	171	211	45.9	12.8
All other types[d]	40	59	32.3	20.4

[a] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[b] Includes anterior, anterolateral, and anteroseptal infarctions.

[c] Includes posterior, posterolateral, and posteroseptal infarctions.

[d] Includes septal infarctions, infarctions characterized by diffuse changes, and infarctions whose site is obscure or unknown, and multiple infarctions at onset.

with "obscure sites," and 9 with "multiple infarctions."

The number of thromboembolic complications developing in patients whose original infarctions were anterior, posterior, or other types is given in Table 106 and Figure 104. The component sections of the bars help the reader to visualize the location of the complications that make up the totals. The actual counts and rates for each location are given in Appendix F, Table 49.

The findings do not suggest that the location of the infarction is of any real importance in complication rates. When the original infarction was posterior in location, the average number of complications per hundred cases was slightly but not strikingly higher than that when the original infarction was anterior (by 13 per cent in the control group and 8 per cent in the treated). These differences were not statistically significant for samples of this size. Moreover, when the rates were restated in terms of number per thousand days observed, they differed even less since patients with anterior infarctions showed a higher death rate than patients with posterior infarctions and therefore had less time in which to develop complications.

Rates for the various component types of complications that made up these total rates were also remarkably similar (see Figure 104 and Appendix F, T

... thromboses and pulmonary emboli in cases having posterior infarctions initially.

The category, all other types, presents more conspicuous contrasts with the other locations than did anterior and posterior, but the directions of the differences were not consistent in the control and treated groups. In view of the mixed character of this third group, its small numbers, and its high death rate (see Chapter XI), any possible conclusions as to the relation of these miscellaneous locations to the complication rate would have little application beyond the particular group involved.

In the absence of further evidence, the data appear insufficient to establish that any relationship exists between the location of the infarction and the probability of thromboembolic complications.

When the various locations are compared with respect to the savings achieved with *anticoagulants, there were likewise no differences* of consequence. Among cases with anterior infarctions at onset, the treated group rate was 29 per cent of the "expected" or control group rate while among cases with *posterior infarctions, the treated group rate* was 28 per cent of the "expected" or control group rate. These differences in rates were both highly significant statistically. *Anticoagulants thus appear to be equally effective in preventing complications among patients with anterior and posterior infarctions.*

Patients with miscellaneous other types of infarctions showed considerably less improvement under anticoagulants. Presumably, *the death rates in this mixed category* were partly responsible since, especially in the treated group, they were considerably higher than in the anterior and posterior groups combined (see Chapter XI), for patients who die early in their illness have correspondingly little opportunity to benefit from anticoagulant therapy. In view of the small and mixed character of this last subgroup, *further speculation is fruitless.*

Complications in Relation to Abnormal Rhythms

Since portions of mural thrombi developing at the site of a myocardial infarction may *become loosened and become emboli* during auricular fibrillation or other cardiac irregularities, the presence of this or other rhythm irregularities during the early part of the illness appeared to offer another possible means for predicting thromboembolic complications. To test this possible approach to prognosis, the incidence of thromboembolic complications among patients with various arrhythmias was analyzed statistically.

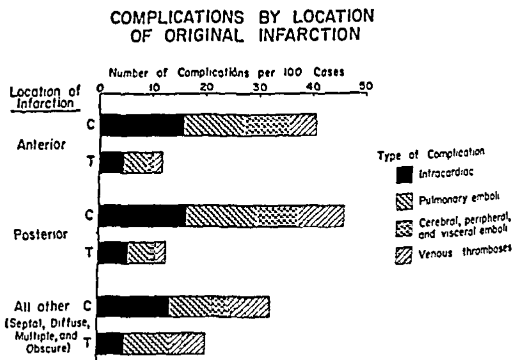


Figure 104. COMPLICATIONS BY LOCATION OF ORIGINAL INFARCTION: Average number of thromboembolic complications of various types developing per hundred cases in the control and treated groups among patients whose original infarctions were in various locations.

The complication rates for cases observed o have had various abnormal cardiac rhyhms during the first week of the illness are shown in Table 107 and Figure 105. Rates are stated in terms of number of thromboembolic complications per thousand days of illness observed since most of the arrhythmias were associated with high death rates which in turn tended to obscure relationships in all rates based on types of counts which make no allowance for reduced exposure to the risk of complications in cases dying. Those interested will find in Appendix F, Table 50 reports of the percentage of cases developing complications and the average number of complications per hundred cases for categories similar to those in Table 107. All the tabulations are confined to the more frequent types of arrhythmias since the number of cases showing the more unusual types of abnormal rhythms were too small for the computation of usable rates. Even for these major types of rhythm abnormalities, conclusions must be considered tentative and suggestive rather than proven because of the exceptionally small samples involved and the impossibility of controlling through standardization relevant related characteristics such as age.

In general, the findings confirm both clinical impressions and previous experience with auricular fibrillation in rheumatic fever cases.[9, 49, 85, 234, 241] Cases in the control group showing auricular fibrillation in the first week of the illness had a complication rate 42 per cent in excess of that for cases showing no arrhythmia. A corresponding comparison for the treated group showed cases with auricular fibrillation to have developed complications more than twice as frequently as did cases with no arrhythmia. *Prompt and adequate anticoagulant protection is thus particularly indicated when auricular*

TABLE 107

[illegible]

Type of Abnormal Rhythm	Number of Cases[a]		Number of Days Observed		Average Number of Thromboembolic Complications[c] per 1000 Days Observed	
	Control Group	Treated Group	Control Group[b]	Treated Group	Control Group[b]	Treated Group
Specific types of abnormal rhythms[d]						
Auricular fibrillation ...	30	39	903	1,341	15.5	7.5
Heart block of any type or degree.	43	60	1,266	1,875	12.7	5.3
Left or right bundle branch block	20	47	683	1,503	7.9	5 3
Premature contractions, ectopic beats or extrasystoles	64	82	2,266	2,895	9.0	3.5
Any type of abnormal rhythm[e]	162	204	5,209	7,023	13.6	4.1
No abnormal rhythm	271	378	10,059	14,648	10.9	3.3

Note *Italics are used when rates quoted are based on less than 30 cases since chance factors render such rates particularly unstable.*

[a] No report on abnormal rhythms was available for 16 cases in the total sample.

[b] Data are corrected for exceptions in treatment For [illegible]

[c] Rates not standardized for age For number [illegible] these categories, see Appendix F, Table 50.

[d] Types of rhythms other than those listed were found in too small numbers to form an [illegible] basis for rates.

[e] Includes any abnormality [illegible] of the schedule, including m[illegible]

fibrillation develops in cases of myocardial infarction.

In contrast to auricular fibrillation, cases characterized by premature contractions, ectopic beats, and extrasystoles showed complication rates that were in essence comparable to those for cases with normal rhythms. The slight differences that were present were not consistent in direction and are believed due to chance. In other words, *the data confirm the usual clinical impression that extrasystoles, premature contractions, and ectopic beats are not associated with an unfavorable prognosis in myocardial infarction, at least in respect to thromboembolic complications.*

Heart block of any type or degree took a position intermediate between these two positions, as is apparent in Figure 105. This category included A-V block of various types, left and right bundle branch block, and dropped beats. In the control group, the heart block group as a whole showed a complication rate 17 per cent higher than that for no arrhythmia and in the treated group, 61 per cent higher. Left and right bundle branch block, a component group of the foregoing, also took an intermediate position in the case of the treated group, but in the control group, showed a rate actually lower than that for no arrhythmia. Since this divergent rate was based on the observation of only 20 cases, its low level probably reflects nothing more than a misleading chance variation. It seems reasonable to conclude tentatively that *heart block also has a mildly unfavorable effect on the prognosis for thromboembolic complications, but the data are less obvious in this respect than, for example, for auricular fibrillation.*

When a single complication rate is computed for all cases in each group showing any type of arrhythmia, the results are similar. *Abnormal cardiac rhythms apparently*

COMPLICATIONS IN RELATION TO ABNORMAL RHYTHMS

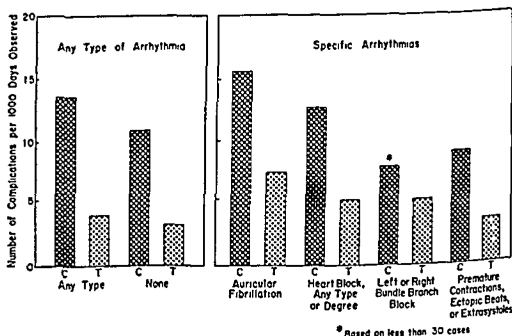


Figure 105. COMPLICATIONS IN RELATION TO ABNORMAL RHYTHMS: Average number of thromboembolic complications per thousand days observed occurring during the six-week period of observation among patients in the control and treated groups showing various types of abnormal rhythms and no abnormal rhythms during the first week of the illness.

do increase the chances of thrombosis and embolism as reflected in the thromboembolic complication rate. The differences are not sufficient to be statistically significant for samples of these sizes, but since this observation is consistent with clinical experience, this lack is no doubt due to the small sample rather than to a lack of a true difference. It would seem that abnormal heart rhythms in general have a tendency to loosen portions of mural thrombi, thus producing systemic or pulmonary emboli. They may also encourage venous thromboses if they are of such a nature that they contribute to the inadequacy of the peripheral circulation.

Finally, the data serve to re-emphasize the almost universal effectiveness of anticoagulant therapy among all subgroups in the sample. Both those showing abnormal rhythms in the first week of the illness and those for whom none was reported for this period developed complications at rates that were only 30 per cent of the corresponding control group or "expected" rates. The differences in both categories were highly significant statistically. While the reductions in the case of the more serious specific arrhythmias were less marked than for the category as a whole, this lesser reduction may reflect little more than the rather obvious fact that persons with these arrhythmias died in greater numbers than others and were thereby prevented from receiving the full benefits of prolonged anticoagulant therapy. *The data do not offer any justification for excluding any patient from anticoagulant therapy because of either the presence or the absence of abnormal rhythms.*

Congestive Heart Failure and Shock in Relation to Complications

Congestive heart failure and shock were the last of the specific conditions to be studied in relation to thromboembolic complications. The basic clinical issue in this instance was. Should anticoagulants be withheld in myocardial infarction cases if heart failure or shock is present? In the chapter on hemorrhagic manifestations (Chapter IX), it will be shown that when congestive heart failure or hepatomegaly are present, the risk of hemorrhage during anticoagulant therapy is somewhat increased. Likewise, some authors have reported a more pronounced prolongation of prothrombin times in response to dicumarol when congestive heart failure or shock is present.[144, 228] [aa] In deciding on the use of anticoagulant therapy in such cases, this increased hemorrhagic risk must be weighed against the probability, suggested [illegible] favor the development of thromboembolic phenomena.[5, 6, 39, 77, 84, 107, 246]

The decision as to the general advisability of anticoagulant therapy in the presence of heart failure or shock must rest on the answer to four questions: (1) What is the relative risk of thromboembolism when congestive heart failure and/or shock are present or not present? (2) Are anticoagulants effective when either congestive heart failure or shock is present? (3) Can hemorrhagic risk be held within reasonable limits under such conditions? (4) Do anticoagulants have any beneficial side-effects in the presence of heart failure or shock? The first two questions are dealt with in the present section. The third will be considered in part in Chapter IX where the percentage of cases bleeding among those who received anticoagulants in spite of the presence of congestive heart failure after the first three days is reported as 18 per cent. Data pertinent to question four have been presented in Chapter VI where the possibility is suggested that anticoagulant therapy may have a beneficial effect on congestive heart failure and shock

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[aa] *The data in the present study failed to demonstrate such a relationship, but it is possible that this was due to a lack of precisely controlled conditions for measuring response or to the smallness of the sample rather than to a lack of a relationship.*

that is independent of its effect on thromboembolic phenomena.

Relation of Congestive Heart Failure and Shock to Thromboembolic Complications

To ascertain whether patients in this series who showed heart failure and/or shock were more or less prone than others to develop thromboembolic complications, patients were classified in two ways: (1) according to their status with respect to heart failure and shock during the first two days after the initial attack, and (2) according to whether they showed congestive heart failure or shock at any time during the second through the sixth week of the illness. The predictive value of these conditions at these two stages of the illness was tested separately.

Classifications based on the patient's status during the first two days were related to the patient's thromboembolic complication rate for the total six-week period. Classifications based on the presence or absence of heart failure and shock during the second through the sixth week naturally could be logically related only to the complication rate from the second through the sixth week. Because of the confusion introduced into case rates by the relatively high death rate among patients suffering from heart failure or shock and the consequent short periods of observation, rates based on the number of days observed are used in this presentation instead of case rates. The rates quoted apply to all days observed and not merely to days when heart failure or shock were actually present since the latter basis for rates was not feasible.[11] The findings resulting from these procedures are reported in Tables 108 and 109 and in Figure 106. Corresponding case rates are given in Appendix F Tables 51 and 52 for the benefit of those who find case rates easier to visualize.

An immediately striking feature of Figure 106 is the great dissimilarity in the prognosis with respect to complications that results from the change in the base period used in the classification. *Initial heart failure and initial shock do not appear to be associated with an unfavorable prognosis as far as thromboembolic complications are concerned. On the other hand, the continuance of these syndromes into the second week or their development for the first time in this later stage appears clearly associated with an unfavorable thromboembolic record.*

Patients with initial heart failure or initial shock actually showed a slightly more favorable complication rate in both the control and treated groups than did those with neither of these conditions initially. The differences are small, however, and not statistically significant. One is puzzled, nevertheless, by the fact that the difference, however small, is in a favorable direction rather than the opposite. Probably the failure of cases with initial heart failure and/or shock to show a relatively unfavorable complication rate can be explained by the fact that these syndromes often clear rapidly. In the present study, among all cases showing initial heart failure in the total sample, this syndrome had cleared within three days in 43 per cent, while an additional 23 per cent had lost the symptoms of heart failure by the end of the first week. Initial heart failure of such short duration had relatively little direct effect on the total complication rate for the six-week period. The possibilities of a relationship were even further reduced by the death within one week of 15 per cent of the patients showing initial heart failure. Whether any other factor also affects the result is not clear. Thus, *the outlook with respect to thromboembolic complications for patients whose initial attack is followed by heart failure or shock or both during the first two days after the attack appears not unfavorable, provided these conditions do not continue*

[11] This lack of refinement was necessary since without very excessive labor, no rates for periods without heart failure could be computed that would apply to days of the illness that were comparable to those on which heart failure was present. Without such rates no valid conclusions would have been possible since the risk of complications varies greatly in relation to the time elapsed after

TABLE 108

COMPLICATIONS IN RELATION TO INITIAL CONGESTIVE HEART FAILURE AND SHOCK: Average Number of Thromboembolic Complications per Thousand Days Observed during the Total Six-Week Period of the Illness in the Control and Treated Groups among Patients with Initial Congestive Heart Failure and/or Initial Shock and among Patients with Neither of These Conditions

Status of Initial Congestive Heart Failure and Initial Shock[a]	Number of Cases		Number of Days Observed		Average Number of Thromboembolic Complications per 1000 Days Observed	
	Control Group	Treated Group	Control Group[b]	Treated Group	Control Group[b]	Treated Group
Initial heart failure present	107[c]	112[d]	3,512	3,633	9.1	4.7
Initial shock present	85[c]	120[d]	2,804	4,036	11.6	3.0
Either initial heart failure or initial shock or both present	161	195	5,385	6,644	10.0	3.3
Neither initial heart failure nor initial shock present	281	394	10,164	15,207	12.9	3.6

[a] Counts include only those cases for whom the reports of heart failure or shock *symptoms* were sufficiently definite to make clear that they occurred during the first two days. They include cases with mild *as well as* severe symptoms, cases whose heart failure symptoms began prior to the initial attack, and cases in which hepatomegalia was the only symptom of heart failure.

[b] Corrected for exceptions in treatment. For method of correction, see Appendix B.

[c] Includes 31 control group cases showing both initial heart failure and initial shock.

[d] *Includes 37 treated* group cases showing both initial heart failure and initial shock.

TABLE 109

COMPLICATIONS IN RELATION TO [illegible]
THE FIRST [illegible]
served in the C[illegible]
Who Survived [illegible]
Shock, or Nei[illegible]

Status of Congestive Heart Failure[a] and Shock after the First Week	Total Cases Surviving to Beginning of Second Week[b]		Number of Days Observed		Average Number of Thromboembolic Complications per 1000 Days Observed	
	Control Group	Treated Group	Control Group[c]	Treated Group	Control Group[c]	Treated Group
Heart failure present	68[d]	97[e]	2,193	2,575	19.7[f]	7.8[f]
Shock present	23[d]	19[e]	373	306	*53.2*	*22.9*
Either heart failure or shock or both present	98	104	2,410	2,762	20.3	7.6
Neither heart failure nor shock present	312	445	10,172	15,054	8.6	2.2

Note. *Italics are used when rates quoted have less than 50 cases as a base since chance factors render such rates particularly unstable*

[a] Includes both left and *right* heart failure, cases with either mild or severe symptoms, and cases with hepatomegalia only.

[b] Counts for the number of survivors in the control group, corrected for exceptions in treatment, are not shown. With this correction, categories totalled 409 instead of 410.

[c] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[d] Includes 13 cases showing both heart failure and shock.

[e] Includes 12 cases showing both *heart* failure and shock.

[f] *Rates* after omission of cases developing heart failure within 2 days *after* a thromboembolic complication and having no heart failure immediately prior to the complication *were 18.1* for the control group and 7.2 for the treated group. There were 82 cases in the control group followed for a total of 2029 days, and 95 cases in the treated group followed for a total of 2305 days who showed heart failure unrelated to complications.

failure and shock do not appear to be good guides for predicting the need for anticoagulant therapy.

The contrast in this respect with the record for the second through the sixth week of the illness is striking (see Figure 106). Patients in the control group with congestive heart failure and/or shock after the first week showed a complication rate about two and one-half times as high as that for patients with neither condition (20.3 *vs.* 8.6). In the treated group, patients with these conditions showed a rate about three and one-half times as high as that for patients with neither (7.6 *vs.* 2.2).

This marked association cannot as yet be said to demonstrate that heart failure and shock predispose to complications since the reverse may have been true, namely that complications, as, for example, new myocardial infarctions or extensions may have precipitated heart failure and shock rather than the reverse. To clarify this question of priority, a further tabulation was undertaken which was limited to cases in which the heart failure preceded the complication or at least appeared not to have been produced by it. In this tabulation all cases whose heart failure had developed within two days after a new complication were eliminated from the rates.

This revision reduced the control group complication rate for cases with heart failure only or heart failure plus shock from 19.7 to 18.1 per thousand days (as compared with 8.6 for patients with neither condition) and the treated group rate from 7.8 to 7.2 (as compared with 2.2 for patients with neither).

COMPLICATIONS IN RELATION TO HEART FAILURE AND SHOCK

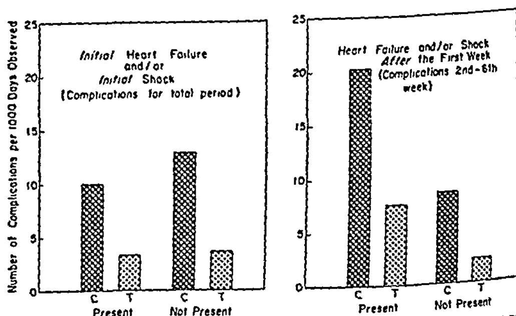


Figure 106. COMPLICATIONS IN RELATION TO HEART FAILURE AND SHOCK: *Average number of thromboembolic complications per thousand days of illness observed in the control and treated groups during the six-week period among patients with and without initial congestive heart failure and/or shock and average number per thousand days observed from the second through the sixth week of the illness among patients in the control and treated groups who survived to the beginning of the second week and experienced or did not experience congestive heart failure and/or shock after the first week.*

A marked contrast thus remains in spite of this refinement.[ii] One must conclude, therefore, *that heart failure and/or shock after the first week, or in other words, persistent heart failure or shock, predispose to thromboembolic phenomena.* This deduction is consistent with the findings of Levinson and Griffith[115] and of Wishart and Chapman[243] who have also noted that patients in heart failure are more than usually prone to develop thromboembolic complications. *The need for anticoagulant therapy for patients whose heart failure or shock fails to clear promptly after the initial attack is obviously urgent*

Physiologically, the association between heart failure and thromboembolic phenomena is probably to be explained in part by the reduced blood flow with stagnation within the lumens of major vessels, reduced concentration of oxygen, and stagnation of the blood within the capillary bed characteristic of heart failure.[kk] The relationship of shock to thromboembolic phenomena is not yet clear The above factors are also present in shock. For both phenomena the association may also be due to a relationship to the size of the original infarction. Large infarctions can be expected both to reduce more radically the work capacity of the heart, with consequent increase in heart failure and shock, and to increase the area of the endocardium particularly suitable to the growth of mural thrombi, with consequent increase in the hazard of embolization. However, mural thrombi sometimes occur overlying the endocardium in rather small areas involved by infarction.

Effectiveness of Anticoagulant Therapy in the Presence of Congestive Heart Failure or Shock

Tables 108 and 109 and Figure 106 may again be consulted to determine whether anticoagulant therapy, which appears to be so much needed by cases with continuing congestive heart failure and shock, is actually effective in preventing thromboembolic complications in such cases. The answer is clear beyond all reasonable doubt. The reductions associated with anticoagulant therapy were substantial in all subgroups. Among cases with either initial heart failure or initial shock or both, the thromboembolic rate in the treated group was only 33 per cent of the control group or "expected" rate, a record of effectiveness only slightly below that for cases with neither condition. When heart failure was tabulated separately from shock, the reduction was found to be somewhat greater proportionately in the case of shock than for heart failure, but in view of the small number of cases with shock only and the complicated relationships under discussion, this difference may be [illegible]

From th[illegible] anticoagul[illegible] effectiveness 'Treated group cases with either heart failure or shock or both any time after the first week showed a thromboembolic complication record that was only 37 per cent of the "expected" or control group rate, whereas treated group cases with neither condition showed a rate 26 per cent of "expected" Thus, while the reductions were again slightly greater in the absence of heart failure and shock, anticoagulants were remarkably effective in preventing thromboembolism even when these conditions were present. In spite of the relatively small samples involved, the difference between the

[ii] A similar refinement was not attempted for shock since the number of cases showing shock from the second through the sixth week was too small in any case to provide a reliable basis for rates.

[kk] These aspects of the etiology of venous thrombosis as a complication of congestive heart failure have been discussed by Loring,[114] particularly as related to venous thrombosis in the upper extremities In the present series only one patient, a patient with prolonged left and right heart failure, who received no anticoagulants, was reported to have shown a thrombosis of the upper extremities This patient showed two such thromboses, one in the jugular vein and one in the left arm.

control group rate of 20.3 complications per thousand days for cases with heart failure and/or shock during this later period and the corresponding treated group rate of 7.6, when tested in the usual manner, was of borderline significance statistically.

This favorable experience with the use of anticoagulants in the present series with patients whose myocardial infarction was complicated with congestive failure confirms that of other investigators who have worked primarily with congestive heart failure rather than with myocardial infarction cases. Anderson and Hull,[4, 6] Harvey and Finch,[61] and Griffith et al.,[77] in reporting on controlled series of congestive heart failure cases, all have noted favorable results associated with anticoagulant therapy as measured in terms of reduced deaths and thromboembolic complications. Jordan et al.[101] and Miller et al.[131] also report finding an association between congestive failure and the presence of intracardiac mural thrombosis and systemic and pulmonary arterial occlusion in 327 myocardial infarction cases studied at autopsy.

The data from the present study, when added to these observations of other investigators, therefore, give a clear answer to the question posed at the outset of this section, namely: Should anticoagulants be withheld in myocardial infarction cases if heart failure or shock is present? *Patients with congestive heart failure or shock have much to gain and little to lose from carefully controlled anticoagulant therapy since* (1) *the risk of thromboembolism in coronary thrombosis is excessive in patients showing heart failure or shock beyond the first week after their attack,* (2) *anticoagulants are almost as effective in preventing thromboembolism in the presence of heart failure or shock as in their absence,* (3) *hemorrhagic phenomena do not constitute an excessive risk with these cases provided anticoagulants are administered with meticulous care.*[ll]

[ll] For discussion of whether other beneficial effects result from anticoagulant therapy in congestive failure cases, see Chapter VI.

CONCLUSIONS REGARDING THROMBOEMBOLIC COMPLICATIONS

The data on complications in the present study can serve a variety of useful purposes. The experience of the control group, for example, can be used[mm] as a picture of the typical incidence of such complications among hospitalized cases of coronary thrombosis with myocardial infarction who survive the first day of hospitalization. When so used, the control group findings serve to highlight the seriousness of the risk of thromboembolic complications in myocardial infarction. The control group rates, when corrected for exceptions in treatment where necessary, were as follows:

1. More than a fourth (26 per cent) developed at least one thromboembolic complication within six weeks of the onset of the attack.
2. Sixteen per cent developed one complication; 5 per cent, two; 4 per cent, three; and one per cent, four complications each.
3. A total of 41.8 thromboembolic complications were diagnosed per hundred control patients.
4. Each hundred control patients showed on the average 15.8 extensions or new infarctions within the heart; 11.6 pulmonary emboli; 4.9 cerebral emboli; 2.7 peripheral and visceral emboli; and 6.8, venous thromboses.
5. During every week through the fourth week after the attack, complications exceeded 6 per hundred control survivors. They reached a peak of 14 per hundred in the second week and declined to less than 3 per hundred after the fourth week.

Since a conservative definition of what constitutes a thromboembolic complication

[mm] Inferences beyond the sample must be qualified with a recognition of the type of sample utilized (see Chapter IV) and of normal sampling error.

was employed,[aa] the degree of risk demonstrated seems obviously such as to warrant all feasible preventive measures.

Extensive statistical analysis by subgroups failed to differentiate any identifiable type of patient who was completely free of thromboembolic complications. In fact, no subgroup of reasonable size within the control group, regardless of the criteria for classification, showed less than 28 complications per 100 patients. It was possible, however, to delineate types of patients who were particularly subject to a risk of complications. For example, the frequency of complications in the control group, as revealed in a variety of measures, was found to be:

1. Greater among patients who had already developed at least one complication than among those who had not yet shown any clinically recognizable complication.

2. Greater among older persons than among younger ones.

3 Greater among persons 10 per cent or more overweight than among those of normal or subnormal weight.

4. Greater among patients considered by the attending physician to be severely ill at onset than among those considered only mildly or moderately ill

5. Greater among patients evaluated as "poor risk" cases than among cases considered "good risk" cases (Russek's criteria[109]).

6. Greater among patients showing congestive heart failure or shock after the first week of the illness than among those without these symptoms or manifesting them in the first week only.

7. Greater among patients showing auricular fibrillation or some type of heart block in the first week than among those with no cardiac arrhythmia in this period.

Similar patterns with respect to relative risk with various types of patients were also generally observed in the treated group, though differentials were frequently of lesser magnitude. Because of this consistency the patterns outlined are believed valid in spite of the fact that the differences (or the size of the samples) were not always sufficiently large to be statistically significant in the technical sense. In neither the control nor treated group did the sex of the patient, the site of the original infarction, or type of hospital care (a possible index of economic status) appear associated in the present sample with a significant difference in the frequency of complications.

The data on clinically diagnosed complications can also be used to evaluate the effectiveness of anticoagulants. Comparisons by treatment groups revealed the following:

1. Considerably less than half as many patients in the treated as in the control group developed at least one thromboembolic complication (10.9 per cent, treated, *vs.* 26.0 per cent, control).

2. Less than a third as many complications per hundred patients developed in the treated as in the control group (13.1, treated, *vs.* 41.8, control).

3. The treated group showed only three-tenths as many complications per thousand days observed as did the control group (3.5, treated, *vs.* 11.9, control).

4. During the first three days of anticoagulant therapy the treated group showed a complication rate per thousand days of therapy that was less than half that of the control group during corresponding days of the illness (7.0, treated, *vs.* 16.4, control).

5. During the period from the fourth day of anticoagulant therapy through four days

[aa] To be considered a thromboembolic complication in statistical counts for this chapter, the complication must have been considered due to a thrombus or embolus, it must have been diagnosed clinically (i e , prior to autopsy), its existence must have been considered definite or probable by the attending physician, and its onset must have occurred within the six-week period of observation.

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2. Less than a third as many complications per hundred patients developed in the treated as in the control group (13.1, treated, *vs.* 41.8, control).

3. The treated group showed only three-tenths as many complications per thousand days observed as did the control group (3.5, treated, *vs.* 11.9, control).

4. During the first three days of anticoagulant therapy the treated group showed a complication rate per thousand days of therapy that was less than half that of the control group during corresponding days of the illness (7.0, treated, *vs.* 16.4, control).

5. During the period from the fourth day of anticoagulant therapy through four days

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after the last dose the treated group showed a complication rate per thousand days of therapy that was less than a fourth that of the rate for the control group during corresponding days of the illness (2.8, treated, *vs.* 12.3, control).

6. The treated group rate was substantially lower than the control group rate for each type of complication. Reductions were the most dramatic, however, for those types of complications usually arising from embolization from mural thrombi (cerebral, visceral, and peripheral emboli); these types showed rates less than a sixth of those for the control group.

7. Regardless of the criteria of classification, all subgroups of any reasonable size showed lower complication rates in the treated than in the control group. When sample sizes were adequate, differences were usually marked and either statistically significant (below 1 per cent level of significance) or borderline (below 5 per cent level of significance).

8. Somewhat greater reductions in proportion to corresponding control levels were usually achieved with anticoagulant therapy among patients with those physical characteristics commonly associated with a good prognosis than among those with abnormal conditions usually considered warning signals of an unfavorable prognosis.[**]

9. Anticoagulants proved about twice as effective when prothrombin levels of 25 seconds or above (23 per cent of prothrombin activity or less) were maintained than when prothrombin levels of less than 25 seconds prevailed.

10. Anticoagulants did not completely eliminate thromboembolic complications at any prothrombin level or for any subgroup of patients regardless of the criteria of classification.

The effectiveness of anticoagulants with various types of patients is summarized in a somewhat different manner in Figure 107 which shows at a glance the decrease in thromboembolic complications relative to the control group found associated with the use of anticoagulants with various types of patients. The downward slanting lines connect in each instance the rate for the control group shown on the left (under the C's with the arrows) with that for the corresponding type of patient in the treated group, shown on the right (under the T's with the arrows). A logarithmic scale is used in order that when drops of the same proportionate amount below the control group level occur, this will be apparent in the similarity in the slant of the lines regardless of actual control group levels. Each of the five sections contains two pairs of lines, one solid and one broken. These pairs represent dichotomous classifications of the cases according to some specific characteristic, as, for example, severe versus mild or moderate at onset in the first section and overweight versus normal or underweight in the second section.

When presented in this manner, the differences in the amounts of reduction achieved in various subgroups, discussed under point 8, appear very minor as compared with the dramatic nature and remarkable consistency of the slopes of these drops below the corresponding control levels, regardless of whether the samples are subdivided by age, sex, weight, type of care, severity, estimate of risk, location of infarction, arrhythmias, or heart failure or shock in the first or later weeks. When judged relative to the control group levels of complication for the same types of cases, the potential benefits of anticoagulants appear remarkably similar for all the major subgroups analyzed. Since, except

[**] In other words, treated group rates were a lower percentage of "expected" (i.e., control group rates) among persons mildly or moderately ill at onset than among those severely ill, lower among persons of normal or subnormal weight than among those ten per cent or more overweight, etc. This pattern was reversed in the sex categories where males, who had a somewhat higher control group rate, showed a greater reduction than females. In the age categories, the greatest reductions were found in the middle rather than in the younger age groups.

for anticoagulant therapy, the control and treated groups were essentially comparable in all respects that might affect complication rates, the above evidence leaves no reasonable doubt that the use of anticoagulant therapy substantially reduces the incidence of thromboembolic complications during the *first six weeks following the onset of coronary* thrombosis with myocardial infarction.

Both the data by individual hospitals and those from other studies further confirm the general effectiveness of anticoagulants. When the data were analyzed by hospitals (as if 16 separate experiments had been made), only one hospital in 16 was found to have shown a less favorable [illegible] exceedingly small). Moreover, every one of the 19 other studies discussed on pages 200–204, reporting on anticoagulant therapy in myocardial infarction using control groups, has reported a better thromboembolic record with than without anticoagulants. Such consistency in the direction of a *difference* is exceedingly rare on a chance basis and is statistically highly significant. The value of anticoagulants in the prevention of thromboembolic phenomena was further confirmed by the autopsy findings which are presented separately in Chapter XIII.

Finally, the data on complications in the present chapter may be used as a basis for the following conclusions regarding the procedures best suited for securing maximum benefits from anticoagulant therapy.

1. Since thromboembolic complications were high during the first week after the attack and reached a peak during the second week, anticoagulant therapy should be begun as soon as possible after the attack and fast-acting anticoagulants (i.e., heparin and/or Tromexan) should be used at least until

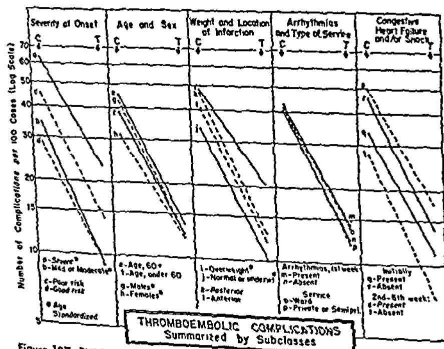


Figure 107. *THROMBOEMBOLIC COMPUCATIONS SUMMARIZED BY SUBCLASSES:* Average number of thromboembolic complications per hundred cases in the control and treated groups contrasted by various subclasses on a logarithmic scale. (For definition of subclasses, see pp. 222–250.)

adequate prothrombin levels can be secured with dicumarol.

2. Since thromboembolic complications remained high for four weeks after the attack, anticoagulants should be continued for at least four weeks, and longer if thromboembolic episodes have intervened. Patients with a record of repeated myocardial infarctions or of repeated thromboembolic complications should be considered for long-term therapy.

3. Patients should be maintained at prothrombin times of 25 to 39 seconds (23 to 11 per cent prothrombin activity) since these times were associated with minimum complication rates. Prolongations beyond these levels gave no additional protection and should be avoided since they involve added risk of hemorrhage.

4. All patients whose prothrombin times can be followed with reliable laboratory tests should receive the benefits of anticoagulant therapy in spite of the absence of warning signals, unless clear medical contraindications are present. This policy is recommended since—

a. All subgroups in the present study showed a sufficient incidence of complications to warrant such therapy.

b. The risk of complications was not found individually predictable.

c. Anticoagulants effectively reduced complications among all types of patients.

5. Special efforts should be made to secure promptly the benefits of anticoagulant therapy for persons of the types found subject to a particularly high incidence of complications (see listing on page 251).

CHAPTER IX

Hemorrhagic Complications

INTRODUCTORY COMMENT

HEMORRHAGE is the only complication of anticoagulant therapy which occurs with any degree either of frequency or of severity. Hemorrhagic complications are encountered during anticoagulant therapy irrespective of whether heparin or dicumarol, or one of their substitutes is used. It is the purpose of the present chapter to evaluate the frequency and severity of bleeding observed clinically in association with anticoagulant therapy. Hemorrhagic findings at autopsy will subsequently be discussed in Chapter XIII.

Basic Contraindications to Anticoagulant Therapy

Hemorrhagic complications of anticoagulant therapy are known to occur more commonly and the bleeding is apt to be more severe in the presence of certain pathological conditions which have come to be considered as contraindications to the use of this type of therapy. As experience with the use of anticoagulants increases, it is evident that these so-called contraindications are such only in a relative sense and that the anticoagulants may be prescribed when one or another of the contraindications exists, provided that the administration of the anticoagulant is done cautiously and with due regard to the meticulous care necessary in this type of therapy. A tabulation of such contraindications, convenient for reference, appears in Table 110. The major conditions which may produce hypoprothrombinemia clinically are shown in Table 111.

Lumbar sympathetic blocks have also been considered dangerous in patients under anticoagulant therapy[41, 143] but Pratt[147] has reported 2,100 sympathetic nerve blocks in 554 patients receiving antithrombotic drugs without a single instance of post-block bleeding. He therefore concludes that "if due precautions are exercised, these two complimentary forms of therapy can be used together safely for the benefit of the patient."

Although anticoagulants are not contraindicated in pregnancy, they should be used here with considerable caution.

Bleeding in the Absence of Major Contraindications

Bleeding during the course of anticoagulant therapy is encountered also in the apparent absence of a contraindication, irrespective of whether heparin or dicumarol is being used. It is fully appreciated that the excessive prolongation of the prothrombin time by the too intensive administration of dicumarol, or of the clotting time of the whole blood by the administration of large doses of heparin, will produce bleeding in a relatively high percentage of cases.

Experience has shown that bleeding in patients receiving anticoagulants may occur in some instances without any apparent explanation; that is to say, when no contraindication can be found and when the prothrombin time in the case of dicumarol, or the clotting time in the case of heparin, is well within the range customarily considered to be therapeutic. Indeed, instances of bleeding following the use of these agents are observed in which, at the time of bleeding, there is no prolongation of the prothrombin or clotting times whatsoever and no explanation as to why the patient has bled other than the fact that an anticoagulant has been administered. *On the other hand, it should not be forgotten that many patients with cardiovascular disease*

perience hemorrhagic episodes, and indeed die from them, in the absence of any anticoagulant treatment.

It has been emphasized repeatedly by those who have acquired the greatest experience with the use of the anticoagulants that bleeding following their administration is uncommon and rarely serious when the drugs are administered according to the meticulous rules developed as our knowledge of these agents has grown. The untoward effects of anticoagulant therapy which have been reviewed in the literature[*] have more often been due to the results of inadequate control of therapy than to the drugs *per se*. This is not to deny that the anticoagulants

[*] For a more detailed discussion of this topic, see Marple and Wright,[122] Chapters 14, 15, and 16.

TABLE 110[*]

CONDITIONS IN WHICH ANTICOAGULANTS MUST BE USED CAUTIOUSLY OR NOT AT ALL

1. Prothrombin Deficiency (Hypoprothrombinemia), or Potential Prothrombin Deficiency.
   a. Vitamin K deficiency.
   b. Severe hepatic disease.
2. Vitamin C Deficiency.
3. Renal Insufficiency.
4. Blood Dyscrasias with Impairment of the Normal Mechanisms for Hemostasis.
5. Interruptions in the Continuity of the Vascular System.
   a. Surgical operations.
      i. Recent operations on the brain and spinal cord.
      ii. Recent surgical operations leaving denuded surfaces.
      iii. Postoperative tube drainage of wounds or viscera.
      iv. Operations performed in the presence of obstructive jaundice, external biliary fistula, or severe liver damage.
   b. Ulcerations and open wounds.
6. Extreme Hypertension.
7. Subacute Bacterial Endocarditis.
8. Dissecting Aortic Aneurysm.

[*] Source: Marple and Wright,[122] p. 100. Modifications have been made in the original list-

TABLE 111[*]

CLINICAL CONDITIONS WHICH MAY PRODUCE HYPOPROTHROMBINEMIA

1. Deficient Availability of Vitamin K.
   a. Inadequate intake (simple dietary deficiency).
      i. Malnutrition.
      ii. Pan-avitaminosis.
      iii. Vitamin K deficient diets—low fat diets.
      iv. Anorexia nervosa.
   b. Interference with synthesis in the intestine.
      i. Administration of certain sulfonamides.
      ii. Hemorrhagic disease of the newborn (?).
      iii. Intrinsic diseases of intestine.
2. Deficient Absorption of Vitamin K.
   a. Absence of bile salts from the intestine.
      i. Obstructive jaundice.
      ii. External biliary fistula.
   b. Interference with digestion of fats.
      i. Pancreatic disease.
      ii. Idiopathic steatorrhea.
      iii. Celiac disease.
   c. Accelerated or interrupted flow of intestinal content.
      i. Chronic vomiting or diarrhea.
      ii. Gastrointestinal intubation.
      iii. Gastrointestinal anastomoses, resections and fistulae.
   d. Loss of normal absorbing surface
      i. Ulcerative colitis, regional ileitis, etc.
      ii. Short circuiting operations and resections.
3. Deficient Synthesis of Prothrombin (Deficient Utilization of Vitamin K).
   a. Diseases of the liver (hepatocellular damage).
      i. Cirrhosis of the liver.
      ii. Primary or metastatic malignancy.
      iii. Acute hepatitis and infectious hepatitis (catarrhal jaundice).
      iv. Acute yellow atrophy.
   b. Experimental.
      i. Hepatic poisons (chloroform, carbon tetrachloride, etc.).
      ii. Partial or complete hepatectomy.
4 Miscellaneous Causes for Hypoprothrombinemia.
   a. Idiopathic hypoprothrombinemia.
   b. Hypoprothrombinemia of the newborn (hemorrhagic disease of the newborn).
   c. Traumatic and hemorrhagic shock.
   d. The effect of certain drugs.
      i. Salicylates.
      ii. Sulphonamides.
      iii. Dicumarol.

[*] Source: Marple and Wright,[122] p. 101.

possess properties which require painstaking care in administration, but very frequently the weakest factor in the use of these agents is the human element, i.e., the failure to obtain adequate laboratory control, carelessness in prescribing the drug, and insufficient attention to the patient and to the course of his prothrombin times, or clotting times, according to the agent being used.

During the course of this study, as reports on individual patients were received in the Central Laboratory, it became apparent to those who reviewed the protocols that episodes of bleeding among the cases so reported were neither frequent, nor were they usually severe in degree. As this observation supported our own experience, it tended to confirm in our own minds the view long held that anticoagulant therapy could be administered without serious hazard of bleeding in the great majority of instances if the administration was cautious and the observation of the patient meticulous, as is the case in the bulk of the cases reported in this study.

A rather striking finding in this study is that bleeding, as defined for this study, usually of a mild or moderate degree, occurred in a number of cases which were not at the time receiving anticoagulants. In fact, such bleeding occurred in not a few patients who did not at any time receive anticoagulant therapy. Such episodes of bleeding were undoubtedly at times the result of thromboembolic complications; on other occasions they represented pre-existing lesions of greater or lesser significance. In other instances, the evidences of bleeding were too minor to be diagnosed as a hemorrhagic complication by the attending physician but under the strict definition adopted was, nevertheless, counted as a bleeding episode in present tabulations. Though such episodes would not actually be considered bleeding in the average clinical practice, they were included because we wished to study the effects of anticoagulants in the greatest detail. Such a study of the treated cases had, of necessity, to be balanced by an equally careful study of control cases. At any rate, it is quite evident that among any large group of patients to whom anticoagulants are administered, there will be some evidences of bleeding during the course of such therapy which should not be ascribed to the anticoagulant per se. Such pre-existing sources of bleeding should, if possible, be determined prior to the institution of anticoagulant therapy lest insignificant bleeding prior to its use be aggravated during, or following anticoagulant therapy. In a similar manner, actual bleeding from potential sources may be precipitated by anticoagulant therapy.

Definition of Episodes

The hospitals participating in this study were instructed to report all hemorrhagic episodes carefully and in detail, in a manner similar to that in which thromboembolic or other complications of the present illness were to be reported. In instances where the report of a case did not provide sufficient detail initially, subsequent correspondence between the Central Laboratory and the hospital from which the report originated usually provided supplementary information sufficient to permit an adequate analysis of the incident in question.

Hemorrhagic complications occurring in cases included in this report during the six-week period of observation, irrespective of the status of therapy at the time the complication occurred, are treated in this section as "episodes of bleeding" for which the following definition has regulated interpretation throughout the analysis:

> *Episodes of Bleeding.* To be included, a bleeding episode must have been diagnosed clinically and must have been observed at least in part during the six-week period of observation. Bleeding from two body orifices was considered two episodes unless both clearly originated from a

temesis and melena). The reappearance of bleeding after the hemorrhagic process had stopped was counted as a second episode. Two or more observations of bleeding were not otherwise counted as two episodes. While in general all evidences of bleeding reported, however small, were included in the counts, certain exceedingly slight evidences of bleeding, e.g., microscopic hematuria when less than 15 erythrocytes were found per high powered field as a maximum, were considered inconsequential and were not, therefore, included as bleeding episodes (see footnote d, pages 259–260).

It would have been difficult to devise any more critical definition which would serve as a practical basis for analyzing bleeding episodes. Review of all the slight evidences of bleeding excluded by the application of the above definition failed to reveal, in any instance, a case of bleeding which could on the one hand be considered of any consequence and on the other be omitted from the tabulation of bleeding episodes according to this definition.

BASIC FINDINGS FOR ALL CASES

The actual clinical findings on bleeding are presented in three major divisions: (1) the basic findings for all cases, (2) findings classified by type of patients, and (3) findings classified by the procedures used for the administration of anticoagulants. The first section on basic findings is in turn subdivided according to the type of data presented.

Number of Episodes of Bleeding

Reference to Appendix F, Table 53 will show that there were a total of 90 episodes of bleeding among the 589 cases in the treated group and, rather surprisingly, a total of 26 bleeding episodes unrelated to anticoagulants[b] among the 442 cases in the control group. Of the former, 54 episodes were probably due to, aggravated by, or precipitated by, anticoagulants, while 36 episodes were probably unrelated to anticoagulant therapy. These last bleeding episodes represent (1) those which occurred in treated patients prior to the prescribing of anticoagulants and which were not aggravated by the subsequent anticoagulant therapy, (2) those clearly due to some known underlying pathology sufficient to explain the occurrence of the bleeding and its full extent and severity (a total of 20 episodes) and (3) those which occurred in patients admitted on odd days (treated group) who did not at any time receive anticoagulants because of a specific contraindication.

For purposes of comparison, these data were analyzed according to the average number of bleeding episodes which occurred for every 100 cases, with the results shown in Table 112 and, graphically, in Figure 108.

The most striking figure is the 5.9 episodes of bleeding completely unrelated to anticoagulant therapy which occurred per 100 cases in the control group. This is in close agreement with the data for the treated group, in which 2.7 bleeding episodes per 100 cases occurred when no anticoagulants

[b] In order that the control group rates cited may represent those that would have prevailed if no exceptions had been made in treatment, all counts and rates reported for the control group in this chapter, unless otherwise specified, exclude 5 episodes of bleeding related to anticoagulants in the control group since exceptions in the usual rule that anticoagulant therapy be withheld from control patients were obviously responsible. These episodes consist of 2 instances of melena (one mild, one moderate), 1 instance of uterine bleeding (mild), 1 sublingual hemorrhage (mild), and 1 postoperative hemorrhage (moderate) To avoid confusion, episodes unrelated to anticoagulants but occurring during anticoagulant therapy of control group patients are also reported throughout (unless otherwise specified) as if they had occurred when no anticoagulants were being given since presumably they would have occurred in any case.

were being given and 3.4 bleeding episodes per 100 cases probably due to other causes occurred during anticoagulant therapy. These two groups among the treated patients total 6.1 bleeding episodes per 100 cases, or almost exactly the same number of episodes per 100 cases that occurred among cases in the control group, completely without any relation to anticoagulant therapy. The two rates for the treated group must be added to secure a total figure for unrelated episodes for the same six-week period covered by the data for the control group. On this basis the difference in the averages for unrelated episodes was not found statistically significant.

Among the cases in the treated group, however, there were an additional 9.2 episodes of bleeding per 100 cases which occurred while anticoagulants were being administered and which were probably related to anticoagulant therapy. This figure is composed of 6.5 episodes per 100 cases due to anticoagulant therapy and 2.7 episodes aggravated or precipitated by anticoagulants. The total of 9.2 episodes per 100 cases thus represents, in all likelihood, the clinical incidence of hemorrhagic complications resulting from anticoagulant therapy in this series.[c] If urine and stool examinations had been done more frequently in the present series, the total probably would have been slightly higher. The total also would have been somewhat higher if more adequate prothrombin times had been consistently maintained. This conclusion is supported by the fact that the bleeding rate for related episodes for the completed study is noticeably higher than that previously reported for the first 800 cases (9.2 *vs.* 7.0).[282, 283] The difference is, in our judgement, to be accounted for in part by the increased doses of *dicumarol* used by physicians as they became more confident in the use of the new therapy and in part by the emphasis placed during the course of the study on repeated urine and stool examinations and on adequate prothrombin levels. This interpretation is consistent with the fact that the reported frequency of unrelated episodes also increased as the study progressed.

When both related and unrelated episodes are combined, a total of 15.3 bleeding episodes of all types occurred per 100 cases in the treated group in this study, as compared with 5.9 episodes in the control group (see Table 112). The difference is highly significant *statistically*. There can be no reasonable doubt that anticoagulant therapy increases the incidence of bleeding.[d]

TABLE 112

[illegible]

Status of Anticoagulant Therapy at Time of Onset of Bleeding	Average Number of Episodes of Bleeding per 100 Cases	
	Control Group[a] (442 Cases)	Treated Group (589 Cases)
Episodes occurring when no anticoagulants were being given	5.9	2 7
Episodes occurring under anticoagulants		
Those probably due to, or aggravated by, anticoagulants	—	9 2
Those probably unrelated to anticoagulants	—	3.4[b]
All episodes	5 9	15 3

[a] Data are corrected for exceptions in treatment For this reason no bleeding episodes under anticoagulants are shown in the control group (see footnote a of Table 114)

[b] Two bleeding episodes where the role of anticoagulants is completely unknown are included here.

[c] For equivalent rates that would have resulted if other definitions of the control and treated groups had been used, see Appendix F, Table 2.

[d] A review of the number of bleeding episodes

Cases Bleeding

The same data can be examined from another angle, namely, the proportion of cases showing bleeding clinically any time during the period of observation (as contrasted with the number of episodes per 100 cases). When all episodes including those unrelated to anticoagulants are included, the percentage of the control group showing bleeding becomes 5.2 per cent and that of the treated group, 12.9 per cent. The difference is again statistically highly significant. However, when episodes related to anticoagulants are omitted, the number of cases bleeding in the treated group is reduced to 35, or 5.9 per cent, a figure only slightly above the control group figure of 23 cases, or 5.2 per cent (see Appendix F, Table 57). The difference in this case is minor and not statistically significant. *It therefore seems*

for those episodes which exhibited such slight evidence of bleeding that they were considered inconsequential and were, therefore, not tabulated, revealed that there were 6 such episodes among cases in the control group and 23 such episodes among cases in the treated group. While these figures indicate clearly the tendency for anticoagulant therapy to produce bleeding, they do not in any way suggest a revision of the data as presented in preceding paragraphs. In most instances these inconsequential episodes represented the transient appearance in the urine of a few erythrocytes; in an occasional case, they represented a mild epistaxis or "pink toothbrush." In no instance could the findings be said to represent a true hemorrhagic episode.

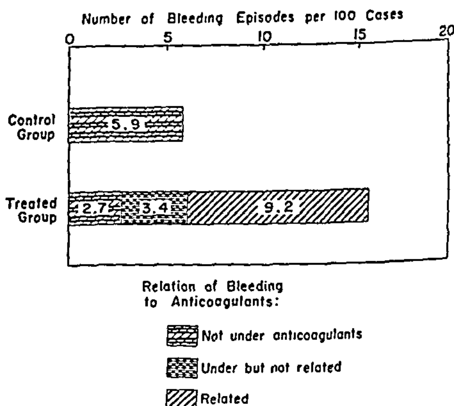


Figure 108. RELATION OF BLEEDING TO ANTICOAGULANT THERAPY: Average number of episodes of bleeding related and not related to anticoagulants per hundred cases in the control and treated groups and status of anticoagulant therapy at time of onset of bleeding.

reasonable to conclude that the difference in total bleeding is due to anticoagulants rather than to any difference between the types of cases included in the two groups.

General Bleeding Experience Compared with That in Other Studies

Comparison of the experience in the present series with that in other studies re-

TABLE 113

C… OTHER SERIES OF MYOCARDIAL …ated Group of This Series and …ulants Were Used in the Treat…ich a Control Group Was Provided

Author(s)	Number of Treated Cases Observed[a]	Number of Cases Bleeding		Percentage of Cases Bleeding	
		Any Bleeding	Severe Bleeding	Any Bleeding	Severe Bleeding
1. This series	589	76	5	12.9	0.8
2. Bresnick et al[32]—Boston City	122	10	3	8.2	2.5
3. Carmichael & Oetting[40]—U. S. Naval Hospital, Long Beach	30	5	1	16.7	3.3
4. Feldman et al[55]—Cook County, Chicago	76[b]	4[b]	—[e]	5.3[b]	0.0[b]
5. Furman et al[60]—Vanderbilt University Hospital, Nashville	74[c]	2	—	2.7	0.0
6. Greisman & Marcus[74]—Lincoln, New York	75	3	—	4.0	0.0
7. Manchester & Rabkin[138d] — Gallinger Municipal, Washington, D. C.	150	16	—[e]	10.7	—[e]
8. Mullins et al[151]—Mercy, Pittsburgh	174	—[e]	2	—[e]	1.1
9. Parker & Barker[177]—Mayo, Rochester	100	8	—	8.0	0.0
10. Peters, Doenges & Brambel[181]—Mercy, Baltimore	110	4	—	3.6	0.0
11. Rashkoff et al[187]—Mount Sinai, New York	142	8	—	5.6	0.0
12. Richter, Del Nunzio & Swiller[191]—Coney Island, Brooklyn	150	7	—[e]	4.7	—[e]
13. Schilling[212]—St Luke's, New York	60	1	—[e]	1.7	—[e]
14. Vander Veer, Marshall & Kuo[231]—Pennsylvania, Philadelphia	35[f]	2	—[e]	5.7	—[e]
15. Zeluff & Field[251]—Bellevue, New York	80[b]	—[e]	—[b]	—[e]	0.0[b]
All series reporting on any bleeding	1694[g]	70	—	8.6	—
All series reporting on severe bleeding	1572	—	11	—	0.7

[a] For specifications regarding exclusion of early deaths from the analysis in these various series, see footnote a, Table 124, Chapter XI

[b] Figure includes cases dying within 48 hours.

[c] Number of cases observed differs from that in Table 124 since the above quoted bleeding rate was based on a mimeographed report appearing prior to publication[79] and supplemented by correspondence with the authors The published report[80] included additional cases but bleeding rates were not given. See also footnote c, Table 93 and footnote e, Table 124.

[d] Some of the patients in this study were treated at home.

[e] Data are not reported.

[f] Data include cases from this hospital included in the present (American Heart) series.

[g] Corrected for duplicate reporting of cases in the present (American Heart) series.

ported in the literature helps to place these findings in perspective. Table 113 was designed for this purpose. It is based on a review of the same 21 other controlled studies of anticoagulant therapy in myocardial infarction that have been listed in connection with comparisons for thromboembolic complications and deaths. The criteria for inclusion in this listing have been outlined in Chapter VIII, page 202. The present table actually includes, however, only 14 studies from the literature since the remaining 7 gave no report on the number of cases bleeding.* Contrary to other comparisons, however, the table includes no data on bleeding in the control groups since this figure was not reported in most of the studies. The table reports two types of figures: first, the percentage of treated cases showing any bleeding and second, the percentage of such cases bleeding severely. Not all 15 series give both these figures. In a few instances, where necessary, published information has been supplemented with further information from the authors.

In general, the studies do not specify the extent to which very minor evidences of bleeding were reported, the frequency of laboratory checks for microscopic hematuria and melena, the length of the period of observation, whether bleeding unrelated to anticoagulants was excluded, and whether hemorrhages found at autopsy were included. Precision in comparison is thus not feasible.

In spite of these uncertainties, Table 113 is useful in placing the general experience of the present study in relation to usual levels as reported by others. Only one study reported a percentage showing any bleeding that was higher than that for the present study. This was a very small series covering only 30 cases and 5 instances of bleeding. In the 12 other studies reporting on bleeding of any type, the percentage of cases bleeding ranged from a low of 1.7 per cent (Schilling) to a maximum of 16.6 per cent (Carmichael and Oetting). Among all other studies pooled, 6.3 per cent showed some hemorrhage, including mild bleeding—a level only about half that for the present study (12.9 per cent). Even including the present study, the pooled figure was only 8.6 per cent. *These other studies, therefore, serve to give further reassurance that the hemorrhagic risk with anticoagulants is not excessive.* Moreover, this low rate cannot be attributed to the particular series included in Table 113 since the 6.3 per cent rate (omitting the present study) is almost identical with the findings of Barker et al.[11] for 1000 surgical patients (6.4 per cent). It is also close to the bleeding experience of many others as reported in the literature (see Marple and Wright,[172] pages 150–152).

The reason for the relatively high level of bleeding in the present study cannot be demonstrated statistically because of lack of comparative data. Various explanations are, however, plausible, as for example: (1) the emphasis placed in the present study on careful observation for minor hemorrhages, especially microscopic hematuris, (2) the relatively inclusive concept in the present study of what constitutes a hemorrhage, and (3) the relatively long period of anticoagulant therapy used. Perhaps the prolongation of prothrombin time was also greater in the present study than in other series. *In any case, the data suggest that the risk of hemorrhage as estimated from the present study is high rather than low in relation to the reported experience of others using control groups.*

Cases showing severe bleeding in the present study will be discussed in detail at a later point (pages 270–272). At this point, it is of

* In addition to the 14 included in Table 113, Loudon, Pease and Cook[155] state in their report that "no complications resulted from anticoagulant therapy." Kerwin[104] in a study published subsequent to this tabulation, reports that 18 6 per cent of his treated cases showed some evidence of bleeding. In the majority of instances the bleeding was in the urinary tract. Kerwin included many cases which showed only a positive chemical test for blood. Bleeding in these instances was of no significance. No comparative study of bleeding in the control group was made

interest to note that the proportion of cases showing severe bleeding in the present study (0 8 per cent) is closer to the combined rate for other studies (0 6 per cent) than was the proportion showing any bleeding.

When the various studies are considered individually, three are found to have shown a higher percentage with severe bleeding than did the present study (see Table 113). The rates ranged from none to 3.3 per cent. This maximum figure is based on a small sample (30 cases) and actually represents only one case of bleeding. Seven studies, on the other hand, showed no severe bleeding whatsoever.

Among all the studies (including the present series) reporting on severe bleeding, only 11 cases from a total of 1572, or 0.7 per cent, showed severe bleeding. In 4 of these cases, the hemorrhages were considered by the authors to have contributed to the death of the patient.[f]

While the percentage of cases showing severe bleeding in the present study (0.8 per cent) was close to the experience in other controlled studies, when judged by the pooled figure of 0.6 per cent, its position changes when comparison is made with experience reported without systematic study of control groups. It is very much less, for example, than the figure of 10 per cent reported by Nichol[118] for cases showing major bleeding in his own practice where he administers dicumarol widely and "pushes" dosage. It is also less than half as high as the figure of about 2 per cent that has been variously quoted[54, 102, 107] as typical of the percentage of cases showing major bleeding under dicumarol. Quotation of this figure of 2 per cent has been based on a review of the literature reporting experience with dicumarol,[g] and on a mailed questionnaire sent to 200 physicians to which 136 physicians replied[116]

The higher level of the 2 per cent figure is probably due to more than one of the following factors: (1) inclusion of many cases treated without adequate caution with respect to prothrombin times, (2) selection of the more dramatic cases for report in print or in questionnaire replies, together with the omission or failure to report experience where no bleeding occurred, (3) the tendency of physicians to select for anticoagulant therapy the more severely ill cases who have at the same time a higher prevalence of various pathological conditions conducive to bleeding (pages 280–284), (4) the inclusion in some reports of hemorrhages found at autopsy, and (5) possible duplication in reporting of the same cases by different respondents answering the questionnaire.

Since an unbiased evaluation of bleeding in anticoagulant therapy must be based on a full consideration of routine uneventful experience as well as of the occasional dramatic episodes, and since it must include experience with all types of cases, mild as well as severe, in reasonable proportion, data in which any element of selection has entered are suspect. On the other hand, the inclusion of autopsy findings is important in the ultimate evaluation of severe hemorrhage but is difficult statistically.

An estimate for the percentage of cases showing severe bleeding in the present study that would include autopsy findings would be about 1.3 per cent.[h] This estimate is lim-

[f] Bresnick et al[12] and Mullins et al[134]

[g] This review of the literature is cited in[11] but the sources are not given.

[h] The estimate given in the autopsy chapter for the average increase in the percentage of cases with hemorrhages or ruptures contributing to death was 1 7 per cent of the cases treated (see p. 440). It assumes that cases dying without an autopsy showed the same proportion of such conditions as those examined at autopsy. If cases with clinically severe but nonfatal hemorrhages [illegible]
to d[illegible]
the [illegible]
gro[illegible]
esti[illegible]
in, [illegible]
in [illegible]
be [illegible]
or [illegible]
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ited to the *increase* above control levels in severe bleeding under anticoagulants. The figure is still below the 2 per cent figure in spite of the fact that it includes an estimated allowance for severe hemorrhages not recognized clinically in cases never examined at autopsy, an allowance which has not, to our knowledge, been made in any other such figure. If, therefore, the 2 per cent figure usually quoted is taken by the reader to imply that the *increase* in bleeding *due to anticoagulants* is of this magnitude, this review of other studies suggests that this figure *is above the level of severe bleeding to be expected when anticoagulant therapy is carefully administered to unselected cases. Because of differences in the concept of what is severe, the handling of autopsy findings, chance, etc., quotation of any specific figure is hazardous.*

Single and Multiple Episodes of Bleeding

Because of the usual method of reporting bleeding, comparison of the bleeding experience with that in other studies must, in general, be confined to data on the percentage of cases showing bleeding. In the present study, counts of bleeding episodes were emphasized. These were analyzed in a variety of ways in the remainder of the present chapter.

The occurrence of multiple episodes is of special interest. Twenty cases, or 4 5 per cent of those in the control group, exhibited a single episode of bleeding, while 3 cases, or 0.7 per cent of the group, exhibited two episodes of bleeding distinct in time. None showed three episodes. It will be recalled that repeated bleeding was not counted as a second episode unless there was clear evidence that the first episode had subsided before the second began. Among the 589 cases in the treated group, 63 cases, or 10.7 per cent of those in the treated group, exhibited a single episode of bleeding; 12, or 2.0 per cent, exhibited two distinct episodes; and a single case (0.2 per cent) experienced three distinct episodes. These percentages are charted in Figure 109. The great major-

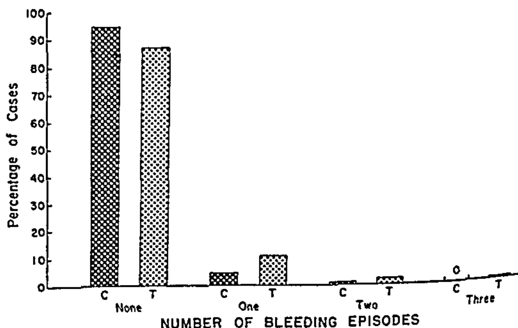


Figure 109. FREQUENCY OF BLEEDING OF ALL TYPES: Percentage of cases in the control and treated groups showing various numbers of bleeding episodes and no bleeding episodes during the six-week period of observation.

ity of multiple bleeding episodes in both the control and treated groups included one or more episodes of hematuria or melena which were of minor consequence.

Figure 109 particularly emphasizes the percentage showing no bleeding (94.6 per cent of the control group and 87.1 per cent of the treated group). This difference is highly significant statistically. *Again, it is clear that bleeding is more frequent under anticoagulants than without them.* Nevertheless, while bleeding episodes, especially multiple episodes, were more frequent in the treated group than in the control, it must be emphasized that a very large proportion of both groups completed the period of observation with no evidence whatever of bleeding.

Types of Bleeding

Episodes of bleeding which complicate the administration of anticoagulants are most apt to be episodes of hematuria, most commonly microscopic, occasionally gross. Bleeding from other sources is not only less frequent, but is more apt to be explainable on the basis of a pre-existing local lesion or some coexisting systemic disease. In this respect, the experience in this study confirms in general previous observations.

The average number of episodes of bleeding per 100 cases of each type and the relation of such episodes to anticoagulant therapy are summarized in Table 114 and, graphically, in Figure 110. Actual counts are found in Appendix F, Table 53.

Hematuria

Among the 442 patients in the control group, 1.4 episodes of hematuria occurred per 100 cases. In every instance this bleeding was microscopic. (For an episode of microscopic hematuria to be included, at least 15 erythrocytes per high-powered field must have been reported.) Among the 589 patients in the treated group, 7.0 episodes of hematuria occurred per 100 cases. The difference between the two groups (when restated in terms of the proportion of patients showing

TABLE 114

TYPES OF BLEEDING: Average Number of Episodes of Bleeding of Various Types per Hundred Cases in the Control and Treated Groups and *Relation of Episodes* to Anticoagulant Therapy

Type of Bleeding	Average Number of Episodes of Bleeding per 100 Cases			
	Control Group[a] (442 Cases)	Treated Group (589 Cases)		
		Total Episodes	Episodes Probably Unrelated to Anticoagulant Therapy[b]	Episodes Probably Due to, or Aggravated by, Anticoagulant Therapy
Hematuria, total	1.4	7.0	2.2	4.8
Microscopic	1.4	5.3	1.8	3.4
Gross	—	1.7	.4	1.4
Hemoptysis	2.5	2.6	2.0	.5
Hematemesis and/or melena	1.8	3.2	1.5	1.7
Epistaxis	—	1.5	.2	1.4
Other	.2	1.0	.2	.8
All episodes	5.9	15.3	6.1	9.2

[a] Excludes 3 episodes of bleeding believed due to [illegible]

hematuria) namely, 1.4 and 6.6 per cent respectively, is highly significant statistically.

Of episodes in the treated group, 5.3 per 100 cases were microscopic and 1.7, gross. Two and two-tenths episodes of hematuria per 100 cases, of which 1.8 were microscopic and 0.4 were gross, were believed probably due to causes other than anticoagulants, while 4.8 episodes of hematuria per 100 cases, of which 3.4 were microscopic and 1.4 were gross, were probably due to, or aggravated by, the use of anticoagulant therapy. In actual numbers, the number of episodes of gross hematuria in the entire series was 10, all of which occurred in cases in the treated group. Two episodes of gross hematuria were probably due to causes other than anticoagulants and 8 were attributed to the effects of anticoagulant therapy.

Figure 111 presents a case of microscopic hematuria due to dicumarol in which the patient appears to have an exaggerated reaction to the drug. Excessive prolongation of prothrombin clotting time at levels of from 60 to 94 seconds[1] resulted in the appearance in the urine of a shower of erythrocytes. Beyond withdrawal of the drug, no specific treatment was given. The hematuria cleared spontaneously without further attention and no further bleeding occurred when dicumarol was resumed.

That every instance of hematuria occurring in a patient receiving anticoagulants was not due exclusively to the effects of the drug is evident from ancillary information obtained from the individual records of cases so treated. Figure 112 presents a case which is thought to demonstrate the role of hepatic disorder in producing an exaggerated response to dicumarol. This patient had a grossly enlarged liver, though a battery of liver function tests proved to be normal. In

[1] These prothrombin times and those in Figure 111 are unconverted times since the conversion of extremely prolonged times for this hospital presented usual difficulties. The converted equivalents for selected times in the lower ranges are given in Appendix F, Table 75 The lack of converted times exaggerates the prolongation

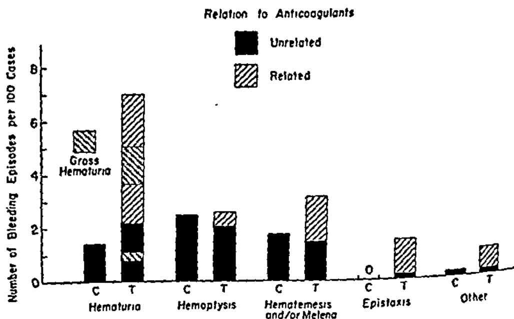


Figure 110. TYPES OF BLEEDING: Average number of bleeding episodes of various types per hundred cases in the control and treated groups, by relation of episode to anticoagulant therapy.

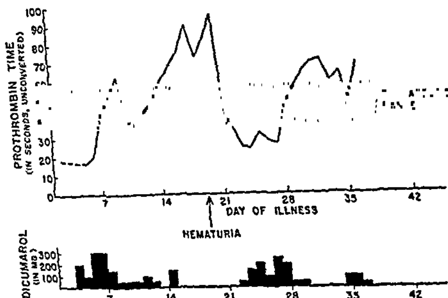


Figure 111. HEMATURIA DUE TO DICUMAROL IN HYPERREACTOR: Case of transient hematuria occurring upon excessive prolongation of prothrombin time in patient with anterior coronary occlusion. (Reaction is overstated by use of unconverted times; see footnote i, p. 266.)

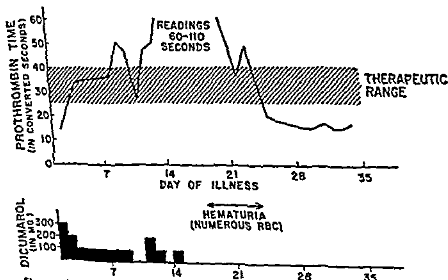


Figure 112. HEMATURIA DUE TO DICUMAROL IN THE PRESENCE OF HEPATOMEGALY: Case of excessively prolonged prothrombin times in the presence of hepatomegaly follow...

spite of relatively low doses of dicumarol, this patient's prothrombin time became excessively prolonged and remained over 60 seconds for about a week despite the withdrawal of dicumarol. During this time a shower of erythrocytes appeared in the urine. After the return of prothrombin times to normal, the hematuria cleared without treatment other than cessation of dicumarol therapy.

Among the patients who suffered hematuria probably due to, or aggravated by, anticoagulants, of which there were 28 such episodes, notes appended to the reports from the participating hospitals indicated that renal pathology existed in at least 4 such cases. From the data, one may safely conclude that in this series less than 5 episodes of hematuria per 100 cases receiving anticoagulant therapy were produced or aggravated by anticoagulants and that such hematuria was gross in no more than 14 episodes per 100 cases under treatment.

That the drugs "were put to the full test" in this connection in at least some instances is demonstrated by one patient from The New York Hospital who exhibited a whole barrage of renal and urinary tract disorders to account for a constant and persistent microscopic hematuria which was only modestly aggravated during anticoagulant therapy. The essential data on this patient, who represents a therapeutic achievement of no mean degree, are shown in the accompanying Figure 113. Limiting discussion to the kidneys and urinary tract, it is to be noted that the patient had had a renal calculus in the left kidney, with hydronephrosis and

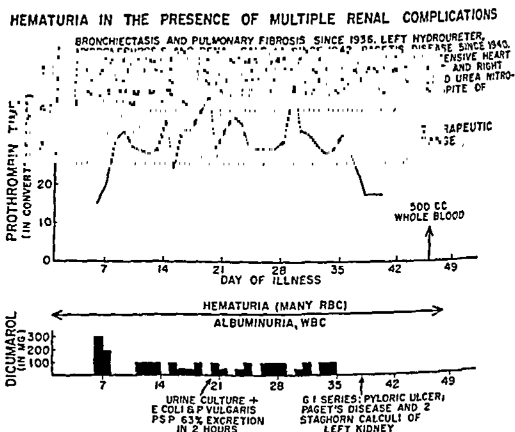


Figure 113. HEMATURIA IN THE PRESENCE OF MULTIPLE RENAL COMPLICATIONS: Case in which dicumarol was administered to a patient with anterior coronary occlusion despite multiple complicating pathological conditions. Adequate prolongation of the prothrombin time was maintained for over one month without aggravating pre-existing hematuria or producing other hemorrhage.

hydroureter, since 1942; he had experienced a prostatectomy for carcinoma in 1945; he had chronic pyelonephritis; and arteriosclerotic hypertensive heart disease had had existed for some years. Upon hospital entry there were symptoms and signs of severe heart failure with associated shock. The urine contained at all times albumin and numerous erythocytes and leukocytes. Urine culture during hospitalization revealed a growth of E. coli and of Proteus vulgaris. PSP excretion was 63 per cent in two hours. The blood urea nitrogen varied between 24 and 36 mg. per cent. The presence of two staghorn calculi in the left kidney was confirmed radiologically. Despite these and other pathological findings, anticoagulant therapy was administered successfully and without apparent complications. His prothrombin times were maintained for the most part within the therapeutic range. There was no bleeding outside the urinary tract and the number of erythrocytes in the urinary sediment did not increase during anticoagulant therapy. The patient recovered from his coronary thrombosis with myocardial infarction.

Hemoptysis

The incidence of hemoptysis which can be ascribed to the effects of anticoagulant therapy is insignificant, being only 0.5 episodes per 100 cases, or a total of only 3 episodes in the entire series of 589 treated cases. Among the treated cases, the actual number of episodes of hemoptysis ascribed to causes other [illegible] the figures were 2.5 and 2.0 and in terms of total episodes, 2 5 and 2 6 in the two groups respectively. The difference (restated in terms of the percentage of cases showing hemoptysis, namely, 2.3 and 2.6 respectively) was not statistically significant.

Hemoptysis is the only category of bleeding in which causes other than anticoagulants clearly and distinctly outweigh the effect of anticoagulant therapy. The explanation for this is quite simple, namely, that among the patients who make up the study, hemoptysis most often represents one of two common complications of acute coronary occlusion with myocardial infarction—chronic passive congestion of the lung or pulmonary embolism. In at least one case in which hemoptysis was aggravated [illegible] ing [illegible] to [illegible] instances in which hemoptysis appeared after the introduction of anticoagulant therapy or in which hemoptysis was aggravated by such therapy were cases in which such pulmonary complications *preceded* the use of this therapy.

Hematemesis and Melena

Episodes of hematemesis and/or melena occurred among the control patients at the rate of 1.8 per 100 cases; they occurred among the treated patients at the rate of 3.2 per 100 cases, of which 1.5 episodes per 100 cases were ascribed to causes other than anticoagulant therapy. Only 1.7 episodes of hematemesis and/or melena per 100 cases among the treated patients were probably due to, or aggravated by, anticoagulants. In actual numbers, 8 episodes of hematemesis and/or melena occurred in the control group and 19 such episodes, in the treated group, of which 9 were probably not related to anticoagulant therapy and 10 were probably due to, or aggravated by, such therapy.

Among the patients who suffered episodes of hematemesis and/or melena probably *due to*, or aggravated by, anticoagulant therapy, at least 5 were known and reported by the observing physician to have a lesion of the gastrointestinal tract which was thought *clinically* to be related to the occurrence of such bleeding. These lesions included two instances of hemorrhoids, one peptic ulcer, one duodenal ulcer and one carcinoma of the sigmoid. In addition, the

spite of relatively low doses of dicumarol, this patient's prothrombin time became excessively prolonged and remained over 60 seconds for about a week despite the withdrawal of dicumarol. During this time a shower of erythrocytes appeared in the urine. After the return of prothrombin times to normal, the hematuria cleared without treatment other than cessation of dicumarol therapy.

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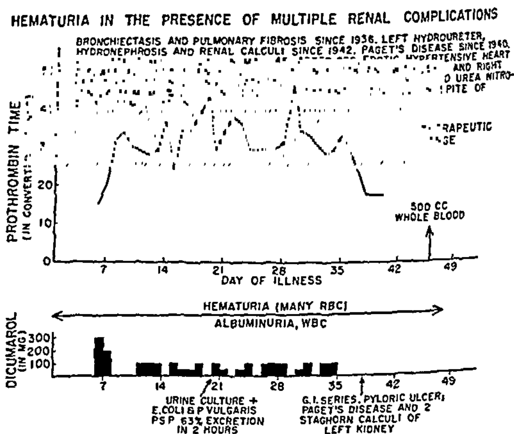


Figure 113. HEMATURIA IN THE PRESENCE OF MULTIPLE RENAL COMPLICATIONS: Case in which dicumarol was administered to a patient with anterior coronary occlusion despite multiple complicating pathological conditions. *Adequate prolongation of the prothrombin time was maintained for over one month without aggravating pre-existing hematuria or producing other hemorrhage.*

severity. Severity was medically evaluated on the basis of the original reports from the hospitals and supplementary correspondence as to the amount of blood loss, the duration of the bleeding, the amount and type of treatment required to stop the bleeding, and whether a threat to life was involved. The findings on severity have already been referred to briefly in the discussion of other studies (pages 261–264). They are given in detail in Appendix F, Table 54 and are shown graphically in Figure 114.

Among the cases in the control group, all 26 episodes of bleeding were reported as being either "mild" or "moderate" in severity. None was severe. In percentage distribution, 69 per cent of these episodes were "mild" and 31 per cent were "moderate."

Among the cases in the treated group, 84 episodes of bleeding, or 93 per cent of those reported, were either "mild" or "moderate" and 5 episodes, or 6 per cent of those reported, were "severe." In one instance the degree of severity was not reported, and could not be ascertained in retrospect.

Within the treated group, there were 36 episodes of bleeding which were unrelated to anticoagulant therapy. Thirty-four of these, or 94 per cent of those within this category, were either "mild" or "moderate," while 1 episode, or 3 per cent of the total, was "severe." The 1 episode, the severity of which is unknown, is included in this category of unrelated episodes. Both the severe hemorrhage (melena and hematemesis) and the episode of unknown severity (also hematemesis and melena) occurred in cases denied anticoagulants because of

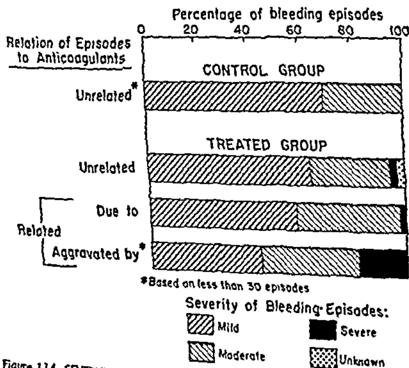


Figure 114. SEVERITY OF BLEEDING EPISODES: Percentage of total bleeding episodes in the control and treated groups that were mild, moderate, or severe, by relation of episode to anticoagulants.

case cited for his numerous urinary tract disturbances in the section on hematuria was shown also to have a pyloric ulcer when a gastrointestinal series was performed at the termination of his anticoagulant therapy.

Another case, about which no comment was made by the reporting physician, was that of a patient with a hiatus hernia who had experienced sufficient loss of blood prior to the present illness to present a significant degree of anemia upon entry to the hospital. When this patient had been on adequate anticoagulant therapy for nearly two weeks, the stools became guaiac positive. Small transfusions were given repeatedly over the course of more than a week, correcting the anemia and apparently diminishing the loss of blood despite the continuation of anticoagulant therapy.

Epistaxis

There were no instances of epistaxis reported for cases in the control series, but there were 9 episodes, or 1.5 for every 100 cases, reported among the cases in the treated group. Most of these were considered to be due to, or aggravated by, anticoagulant therapy.

One is tempted to believe that there was, in many instances, a failure of the observing physician to report episodes of epistaxis, especially when these were mild or moderate in degree. So many elderly persons suffer from periodic attacks of epistaxis, even when bedridden and quiet, that it seems improbable that not one of the 442 patients in the control group ever exhibited this symptom. On the other hand, and particularly to those who suffer epistaxis repeatedly, the symptom is apt to be inconsequential, not to be remarked upon, and readily and unwittingly hidden by the disposal of evidence. This is true, in general, of bleeding from the nose only since bleeding from other body orifices, especially by bedridden patients, is difficult or impossible to hide. Furthermore, episodes of bleeding from other sites are more apt to be a concern to the patient and, therefore, a cause for disclosure even if not observed by the attending staff.

Other Types of Bleeding

In actual numbers, there was but a single episode of bleeding of a type other than those enumerated previously among the cases in the control group and only 6 episodes among the cases in the treated group. In terms of episodes of bleeding per 100 cases, the figures were 0.2 for the controls and 1.0 for the treated cases. Of the latter, 0.8 episodes per 100 cases were probably due to, or aggravated by, anticoagulant therapy.

Among the cases in the treated group for which 5 episodes of bleeding due to, or aggravated by, anticoagulants were described, 2 exhibited pathological lesions from which bleeding occurred. One of these bled postoperatively after closure of a slough secondary to a hypodermoclysis. Anticoagulant therapy was discontinued before operation. The second bled from an old scar on the lip.

The number of cases bleeding from miscellaneous sources and the number of episodes of such bleeding was so small as to be, in numbers at least, inconsequential. This low incidence occurred in spite of the fact that a considerable number of cases in this series were operated on during the course of the present illness and not always in the absence of anticoagulant therapy. In the list of operations performed on cases in this series anticoagulant therapy was often given postoperatively if not before. In only one instance did postoperative bleeding related to anticoagulants occur, namely, in the case cited in the preceding paragraph, even though postoperative bleeding into an incision is ordinarily thought of as being one of the more common types of hemorrhage encountered in using anticoagulants.

Severity of Bleeding Episodes

In addition to classification by type, episodes of bleeding were classified as to

unrelated to anticoagulants becomes 1.6 per 1000 days in both the control and treated groups, 1.1 episodes being mild and 0.5 episodes, of moderate severity for both groups. The rates are given in Appendix F, Table 55 and shown graphically in Figure 115. (Figure 115 shows rates to 2 decimal places, hence bar for control is slightly longer than that for treated.) Closer comparability could not be hoped for. The only differences between the two groups were an additional single severe episode and a single episode of unknown severity in the treated group. The severe bleeding episode consisted of hematemesis and melena occurring in a patient with peptic ulcer, *who was denied anticoagulants because of this ulcer.* The bleeding of unknown severity also consisted of hematemesis and melena in a patient *also denied anticoagulants* because of another episode of this type of bleeding occurring immediately before the onset of the coronary attack.[j]

When attention is turned to episodes due to, or aggravated by, anticoagulants, the appropriate base is total days of anticoagulant therapy instead of total days of observation, as used for unrelated episodes.[k] The rate on this basis is 3.3 bleeding episodes

[j] For explanation of inclusion of these cases in the treated group, see Chapter III.

[k] Since each case contributes to the rate base in proportion to the period of time he was actually observed (or treated) instead of equally as in case rates, distortion might be introduced in such rates if selected types of patients were treated for extra long or extra short periods of time. This source of bias is minimized in the present study by the fact that practically all patients surviving were observed six weeks and four weeks was the recommended length of anticoagulant therapy.

RATE OF MILD, MODERATE, AND SEVERE BLEEDING

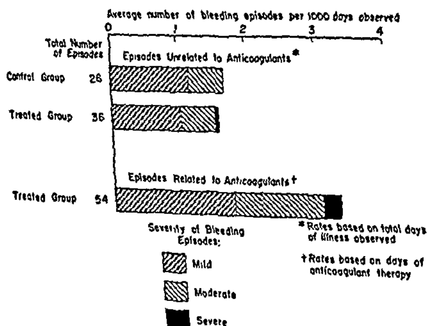


Figure 115. RATE OF MILD, MODERATE, AND SEVERE BLEEDING: Average number of mild, moderate, and severe bleeding episodes *unrelated* to anticoagulants per thousand days of illness observed in the control *and treated* groups and average number of bleeding episodes *related* to anticoagulants in the *treated* group per thousand days of anticoagulant therapy.

contraindications. When these were excluded, the severity of unrelated hemorrhages in the control and treated groups was almost exactly similar.

In addition, 54 episodes of bleeding which were probably due to, or aggravated by, anticoagulant therapy occurred in the treated group. Fifty of these, or 93 per cent of those within this category, were either "mild" or "moderate" (54 per cent, mild; 39 per cent, moderate), while 4 episodes, or 7 per cent, were "severe." Of the 4 severe episodes of bleeding related to anticoagulant therapy, 1 in 589 patients (a case of gross hematuria) was probably due to anticoagulants. The other 3 severe bleeding episodes (2 gross hematuria and 1 gross melena) were probably merely aggravated by the use of anticoagulants. The proportion of severe episodes in the aggravated category (19 per cent) was considerably higher than the proportion of severe in the "due to" category (3 per cent) but the numbers involved are, of course, small. None of the hemorrhages diagnosed clinically contributed to the death of the patient. Some diagnosed only at autopsy were, however, the primary or contributing cause of death. These are discussed in Chapter XIII.

It is evident from these data that anticoagulant therapy not only increases the number of episodes of bleeding but that the severity of bleeding tends to be greater among those episodes due to, or aggravated by, anticoagulants than among episodes of bleeding unrelated to anticoagulant therapy. In spite of this increase, however, only 0.8 per cent of the treated group showed severe bleeding during the period of observation.

The fact that "severe," "serious," and even fatal episodes of bleeding do sometimes occur in patients treated with anticoagulants is amply confirmed in the literature.[53, 64] *The clinical data obtained in this study indicate, however, that bleeding episodes of a "severe" degree may be amazingly infrequent when anticoagulant therapy is supervised meticulously.* This fact is also confirmed in the literature as was demonstrated in the review of other studies presented in this chapter. It is likewise supported, in general, by the autopsy findings on hemorrhages presented in Chapter XIII.

Bleeding Episodes on a Day-Rate Basis

The incidence of bleeding may also be examined in terms of rates based on counts of patient-days since the opportunity for observing bleeding is closely related to the number of days the patient was observed. It will be recalled that similar day counts were reported for complications (see Chapter VIII). The unit used is again 1000 days of observation or of therapy, as the case may be. Physicians may visualize the concept of 1000 days more readily if this time is thought of as approximately equivalent to a 37 day total period of observation for 27 patients ($27 \times 37 = 999$), or a four-week period of anticoagulant therapy for each of 36 patients ($36 \times 28 = 1008$). Both concepts are realistic since, *because of days lost through deaths*, the average total period of observation for the treated group was about 37 days and the average period of anticoagulant therapy, 28 days. Therefore, to convert day rates into the usual counts in terms of number of episodes per *100* cases, day rates for episodes unrelated to anticoagulants (based on total days observed) should be multiplied by 3 7, and day rates for episodes related to anticoagulants (based on days of anticoagulant therapy) should be multiplied by 2 8. Rates thus converted approximate those previously quoted and have the advantage of increased accuracy since they make appropriate allowance for reduced exposure to risk of hemorrhage due to death before the end of six weeks and for other variations in exposure such as are involved in short or extra long periods of anticoagulant therapy.

Conversion of the findings to a day-rate basis reveals the close comparability between the control and treated groups. With this refinement, the number of bleeding episodes

. . to anticoagulants becomes 1.6 per 1000 days in both the control and treated . , 1.1 episodes being mild and 0.5 episodes, of moderate severity for both groups. The rates are given in Appendix F, Table 55 and shown graphically in Figure 115. (Figure 115 shows rates to 2 decimal places, hence bar for control is slightly longer than that for treated.) Closer comparability could not be hoped for The only differences between the two groups were an additional single severe episode and a single episode of unknown severity in the treated group. The severe bleeding episode consisted of hematemesis and melena occurring in a patient with peptic ulcer, *who was denied anticoagulants because of this ulcer* The bleeding of unknown severity also consisted of hematemesis and melena in a patient *also denied anticoagulants* because of another episode of this type of bleeding occurring immediately before the onset of the coronary attack.[j]

When attention is turned to episodes due to, or aggravated by, anticoagulants, the appropriate base is total days of anticoagulant therapy instead of total days of observation, as used for unrelated episodes.[k] The rate on this basis is 3.3 bleeding episodes

[j] For explanation of inclusion of these cases in the treated group, see Chapter III.

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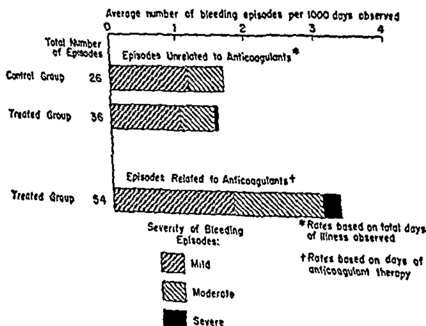


Figure 115. RATE OF MILD, MODERATE, AND SEVERE BLEEDING: Average number of mild, moderate, and severe bleeding episodes unrelated to anticoagulants per thousand days of illness observed in the control *and treated* groups and average number of bleeding episodes related to anticoagulants in the treated group per thousand days of anticoagulant therapy.

related to anticoagulants per thousand days of anticoagulant therapy.[1] By severity, these were distributed as follows: 1.8 episodes mild, 1.3 episodes moderate, and 0.2 episodes severe—the same proportionate distribution by severity as previously reported. These rates are also illustrated in Figure 115. Further supporting details appear in Appendix F Tables 54 and 55. These episodes related to anticoagulant therapy were about twice as frequent as episodes unrelated to anticoagulants (i.e., 3.3 vs. 1.6). Rates for related episodes were higher than those for unrelated episodes in all categories of severity, but especially for episodes of moderate and severe degree. The total rate of 3.3 may be visualized as one bleeding episode related to anticoagulant therapy for each 300 days of therapy, or one episode for each 11 patients treated four weeks with anticoagulants. Severe episodes due to, or aggravated by, anticoagulants were very infrequent—only about 1 per 5000 days of therapy or less than 1 per 100 cases.

When episodes both related and unrelated to anticoagulants were combined for the treated group, the total amounted to 4.1 episodes per thousand days of therapy, of which 2.4 were mild, 1.5, moderate, and 0.2, severe. Even this total rate, which includes unrelated bleeding, is obviously low and amounts to only about one episode to each 9 patients receiving the benefits of anticoagulant therapy, as compared with one to each 17 patients without such therapy. Severe bleeding in the treated group occurred only once for each 118 cases.

[1] These rates include only treated group cases. Control group cases receiving anticoagulants as an exception showed a higher rate of bleeding due [illegible] probably reflect the adverse selection already known to characterize this group (or chance fluctuations). They should not be taken as a reflection of the incidence of bleeding to be expected in an average group when anticoagulants are given.

Bleeding Episodes by Week of Illness

Bleeding Episodes Unrelated to Anticoagulants

In order to ascertain whether the risk of bleeding decreased as the patient recovered from his original myocardial infarction, the average number of bleeding episodes probably unrelated to anticoagulant therapy per 1000 days of illness observed was calculated for each week of the illness for both the control and treated groups. The figures for the two groups week by week were remarkably similar as Figure 116 indicates at a glance. The treated group exceeded the control group during the first, third, fifth and sixth weeks; the control group exceeded the treated group during the second and fourth weeks. Episodes unrelated to anticoagulants were most numerous the first week of the illness (about 5 per thousand days of observation). They were only about one-half as frequent during the second week of the illness and thereafter remained consistently at a low level, never exceeding 1.0. Since these data were based upon episodes classified according to the time they were first reported as observed, they represent the incidence of new episodes and not the prevalence of bleeding at any given time. Many such episodes undoubtedly continued into later weeks. The actual number of bleeding episodes and number of days observed are reported in Appendix F, Table 56.

Episodes Related to Anticoagulants

In contrast to episodes unrelated to anticoagulants, the average number of bleeding episodes probably due to, or aggravated by, anticoagulants per 1000 days of such therapy tended to be rather constant, as Figure 116 also indicates. The actual weekly figures from the first through the sixth week were, in sequence: 3.0, 4.7, 2.6, 2.5, 3.6 and 3.7.

In explanation of the high rate in the second week it should be emphasized that the number of episodes of bleeding were

tabulated by week of *total illness*, and not by week of *anticoagulant therapy*. The fact that most cases did not come under the full influence of dicumarol until the second week may account for the increase in this week. Cases with a condition which predisposed them to bleeding and those in which preexisting bleeding was aggravated by the administration of dicumarol were undoubtedly particularly apt to exhibit hemorrhage promptly after they were brought under the full influence of the drug, especially if they proved to react excessively to small quantities of dicumarol. It is possible, on the other hand, that as Beaumont, Chevalier and Lenègre[11] have suggested, about a week of physiological hypocoagulability follows the infarction and begins on the second or third day. If this is the case, the risk of bleeding under dicumarol would be greatest during this period. Such a physiological pattern could also explain the observations reported.

BLEEDING IN RELATION TO TYPE OF PATIENT

In addition to the foregoing findings that apply to all patients in the series, an at-

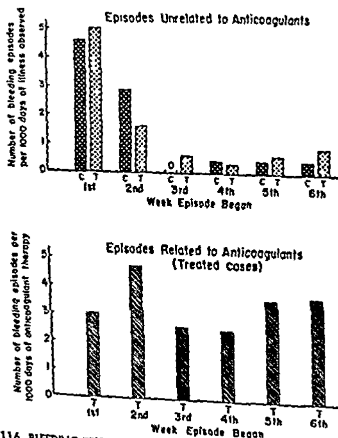


Figure 116. BLEEDING EPISODES BY WEEK OF ILLNESS. Average number of bleeding episodes unrelated to anticoagulants per thousand days of illness observed in the control and treated groups and average number of bleeding episodes related to anticoagulants in the treated group per thousand days of anticoagulant therapy, by week of illness when episode began.

tempt was made to ascertain which types of patients are most likely to bleed. Pertinent for this purpose are, of course, the specific contraindications for anticoagulant therapy already cited (see Table 110). Since these were in general known at the time this study was undertaken, such cases were excluded from anticoagulant therapy at the outset and thus do not furnish information as to the degree of risk involved in the use of anticoagulants in these conditions. The following sections consider variations with age, good and poor risk categories, liver and renal disease, and congestive heart failure.

Bleeding Episodes by Age

In order to ascertain first whether the risk of bleeding varied significantly in relation to the age of the patient, bleeding episodes were analyzed by age. The results are presented in Figures 117 and 118, and are supported by Appendix F Tables 57 and 58. Episodes were divided as previously into those unrelated to anticoagulant therapy and those due to, or aggravated by, anticoagulants. These were analyzed in three ways: percentage of cases bleeding, number of bleeding episodes per 100 cases, and number of bleeding episodes per 1000 days of observation (or therapy).

Regardless of the method of analysis, the variations by age on the whole appear erratic and are probably without medical significance. While the day rates for unrelated episodes perhaps appear on first inspection to show an irregular upward trend, the pooled average for cases under 60 was found to be 1.6 and that for cases 60 and over, 1.8 per 1000 days. The difference is so small that one would not be justified in concluding without much further study that age is related to the risk of bleeding.

Bleeding Episodes in Relation to Good and Poor Risk Categories

A second criterion of possible interest in relation to bleeding is the physician's evaluation of the case as a good or poor risk as

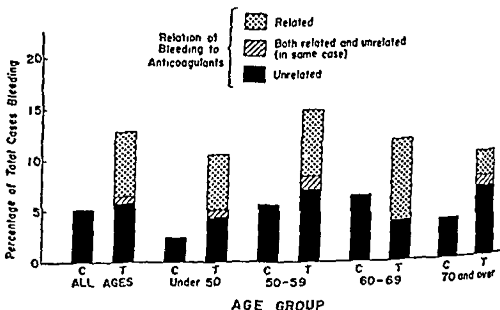


Figure 117. CASES BLEEDING, BY AGE: Percentage of cases in the control and treated groups showing bleeding unrelated to anticoagulants, bleeding related to anticoagulants, and both types, by age.

far as the patient's general prognosis is concerned.

Russek and his co-workers[209] have recommended that only poor risk cases receive anticoagulant therapy since they consider that the risk of severe hemorrhage, estimated by some at about 2 per cent, is too great to be justified for patients so mildly ill that their total death rate is in the neighborhood of 2 per cent. These discussions have ignored, however, the possibility that the incidence of bleeding may also be considerably lower in cases that are good general risks than in those that have a poor prognosis, with the result that the overall rate of hemorrhage visualized in these arguments does not actually apply to the cases under discussion.

To assist in clarifying this issue, the findings for clinically diagnosed bleeding episodes for the present study were analyzed by criteria approximating the general good and poor risk categories of Russek et al.,[209] following procedures described in Chapter VIII. The good and poor risk criteria used apply to the estimated risk of death or thromboembolic complications and apparently *were not* defined with the hemorrhagic risk in mind. The results are given in Table 115 and Figure 119, subdivided according to the severity of the episodes involved. The hemorrhages and cardiac ruptures found at autopsy to have contributed to death (discussed in Chapter XIII) do not appear in these data since they were not diagnosed clinically. There was, however, only one good risk case in this category at autopsy and this case appeared to have shown at the outset various indications of poor risk not included in Russek's criteria, among them a large infarction, hypertension, and an age of 84. In addition, this patient had been classified by the attending physician as severely ill at onset.

As will be noted in Table 115, each of the

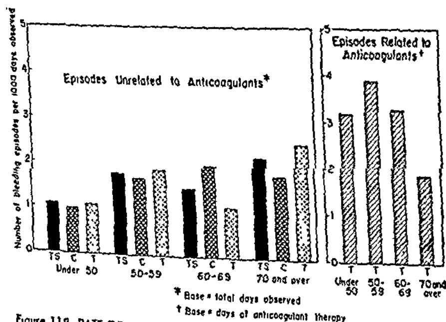


Figure 118. RATE OF BLEEDING EPISODES, BY AGE: *Average number of bleeding episodes unrelated to anticoagulants per thousand days of illness observed in the total sample and in the control and treated groups, and average number of bleeding episodes related to anticoagulants in the treated group per thousand days of anticoagulant therapy, by age.*

TABLE 115

BLEEDING EPISODES IN GOOD AND POOR RISK CASES: Number of Mild, Moderate, and Severe Bleeding Episodes and Average Number per Hundred Cases in the Control and Treated *Groups among Patients Estimated to Have Been Good* and Poor Risk Cases by Criteria Approximating Those of Russek *et al.*[111]

Estimate of Risk and Severity of Bleeding Episode	Number of Bleeding Episodes				*Average Number of Bleeding Episodes per 100 Cases*			
		Treated Group				Treated Group		
	Control Group	Total Episodes	Episodes Probably Unrelated to Anticoagulant Therapy[a]	Episodes Probably Due to, or Aggravated by, Anticoagulant Therapy	Control Group	Total Episodes	Episodes Probably Unrelated to Anticoagulant Therapy[a]	Episodes Probably Due to, or Aggravated by, Anticoagulant Therapy
Moderately strict definition of good risk[b]:								
Good risk cases (control, 65 cases; treated, 114 cases):								
Severity of bleeding episode:								
Mild	—	9	4	5	—	7.9	3.5	4.4
Moderate	1	4	—	4	1.5	3.5	—	3.5
Severe	—	1	—	1	—	.9	—	.9
Total	1	14	4	10	1.5	12.3	3.5	8.8
Poor risk cases (control, 377 cases; treated, 475 cases):								
Severity of bleeding episode:								
Mild	18	43	19	24	4.8	9.1	4.0	5.1
Moderate	7	28	11	17	1.8	5.9	2.3	3.6
Severe	—	4	1	3	—	.8	.2	.6
Severity unknown	—	1	1	—	—	.2	.2	—
Total	25[c]	76	32	44	6.6[c]	16.0	6.7	9.3
Very strict definition of good risk[d]:								
Good risk cases (control, 24 *cases; treated, 47 cases*):								
Severity of bleeding episode:								
Mild	—	4	2	2	—	8.5	4.25	4.25
Moderate	—	—	—	—	—	—	—	—
Severe	—	—	—	—	—	—	—	—
Total	—	4	2	2	*0.0*	8.5	4.25	4.25
Poor risk cases (control, 418 *cases; treated, 542 cases*):								
Severity of bleeding episode:								
Mild	18	48	21	27	4.3	8.9	3.9	5.0
Moderate	8	32	11	21	1.9	5.9	2.0	3.9
Severe	—	5	1	4	—	.9	.2	.7
Severity unknown	—	1	1	—	—	.2	.2	—
Total	26[c]	86	34	52	6.2[c]	15.9	6.3	9.6

Note: *Italics are used when averages quoted are based on less than 50 cases since chance factors render such figures particularly unstable.*

[a] See footnote b, Table 114. [b] See definition on p. 231. [c] See footnote a, Table 114.

[d] Same definition as for moderately strict except that third degree pain was added to the criteria for poor risk.

six possible types of contrasts show the number of bleeding episodes per hundred cases to be lower in the good risk than in the corresponding poor risk category. *The consistency of this pattern clearly suggests that good risk cases have a generally lower hemorrhagic risk than do poor risk cases.* This association of bleeding with poor risk cases seems reasonable *a priori* since cases showing the poor risk criteria would be expected to show also other unfavorable conditions, such as renal and liver disease or impairment, shock and miscellaneous hidden lesions which would precipitate bleeding, to a greater extent than would good risk cases. Episodes of bleeding from such conditions and their aggravation by dicumarol appear to add sufficiently to the totals to produce the observed contrasts. Consideration of details involves a separate review of the findings by two definitions of good risk.

When the moderately strict definition of good risk is used (i.e., 3 degrees of pain permitted in the good risk category), 10 treated good risk cases bled as contrasted with 66 poor risk treated cases (0 per cent *vs.* 14 per cent of these two groups respectively).[a] A contrast by risk categories was also found in the control group (2 per cent, good risk, *vs.* 6 per cent, poor risk). Differences involving episode counts appear in Table 115 and Figure 119.

[a] The chances are slightly less than 1 in 5 that a difference of this amount would occur on a chance basis. If this difference was maintained with a somewhat larger sample of good risk cases, statistical significance at the significance level adopted for the present study could readily be demonstrated.

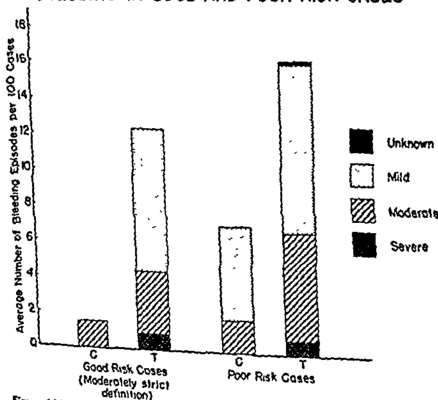


Figure 119. BLEEDING IN GOOD AND POOR RISK CASES: Average number of mild, moderate, and severe bleeding episodes per hundred cases in the control and treated groups among patients estimated to have been good and poor risk cases by moderately strict criteria approximating those of Russek et al.[203]

Of the 15 episodes *occurring in good risk* cases by the moderate *definition, only 1* was severe. This was a *short episode of* bloody stools sufficient in severity to lower the patient's R.B.C. and hemoglobin levels. *This episode* can be attributed to poor management of anticoagulant therapy since no underlying pathology was ever found in spite of a careful search and the episode followed a seven-day sequence during which no prothrombin time shorter than 56 seconds (converted) was reported. These seven days culminated in a three-day sequence during which all prothrombin readings were over 60 seconds (converted) and the patient, notwithstanding, *was given a further dose of 100 mg. of dicumarol.* When treatment was belatedly instituted by withdrawal of dicumarol, plus administration of vitamin K, plasma, and whole blood, the bleeding ceased promptly. *Except for this case of obviously careless management, no severe bleeding was clinically diagnosed in the good risk group by either definition.*

When the stricter definition of good risk was applied (i.e., 3 degrees of pain defined as a poor risk indicator), the two samples became very small. Hence the findings must be considered suggestive only. With this necessary qualification, it is reported that only 3 good risk cases thus defined bled at all. All were treated cases and constituted 6 per cent of the treated good risk group. In contrast, 73 cases (14 per cent) of the treated poor risk group bled. Similarly, 23 of the control poor risk cases bled (6 per cent) but none of the good risk cases. These three good risk treated cases bleeding showed only 4 bleeding episodes, all mild only. Of these, two were due to dicumarol (1 mild episode of epistaxis and 1 mild case of ecchymosis) and two, to other causes. Since all good risk patients by this definition survived the attack, these 4 bleeding episodes (9 per hundred cases in the treated group) constitute the *total* known hemorrhages for this group. Anticoagulant therapy for this same small group was associated with a substantial reduction in thromboembolic co plications (see Table 103, Chapter VII This small increase in mild bleeding appe a small price indeed for a substantial duction in thromboembolic phenomena.

From the consistency and reasonablene of the pattern demonstrated, it seems a propriate to conclude that *the risk of ant coagulant therapy is lower in good than poor risk cases. Such risk as exists for the cases seems to the authors to be clearly ju tified by the associated decrease in the inciden of thromboembolic complications.*

Bleeding in Relation to Liver or Rena Dysfunction and Congestive Hea Failure

Clinical experience has repeatedly demonstrated that in the presence of hepatic o renal dysfunction and sometimes in marked congestive failure and irrespective of the etiology of the condition, the effects o dicumarol are unpredictable and often may be labile or exaggerated. Uncertainty in predicting the patient's response when these conditions are present leads to difficulty in adjusting the dosage in a manner that will [illegible] which in [illegible] re- [illegible] ex- pected in persons with these complications of their illness. In addition, certain renal diseases, and also occasionally congestive failure, are accompanied by hematuria even in the absence of anticoagulant therapy. Aggravation of such bleeding during dicumarol therapy is therefore a reasonable expectation.

Bleeding during Dicumarol Therapy

To determine whether the experience of the present study confirmed these clinical impressions, the number and percentage of patients bleeding during dicumarol therapy was tabulated for those who did and those who did not show azotemia and/or renal disease at any time during the illness. Similar

figures were computed for those showing and those not showing liver enlargement and also for those showing and those not showing congestive failure (other than as an initial symptom). The sample thus analyzed was limited to those cases who received dicumarol for a sufficient period (usually at least nine days) to be usable for the analysis of degree of reaction to dicumarol reported on pages 372-382. The results of the present analysis are shown in Table 116, Appendix F Table 59, and Figure 120.

In spite of the relatively small number of patients having a positive record of these conditions during their illness, the increase *in the* risk of bleeding associated with hepatic or renal dysfunction and congestive failure is very obvious and in accord with the pattern of clinical impressions. Azotemia, with or without accompanying renal disease, showed the highest bleeding record of the conditions tabulated. Thirty-one per cent of the group with this condition bled during dicumarol therapy as compared with 10 per cent of those without this condition. Among those with liver enlargement of any degree, 22 per cent bled during therapy as contrasted with 10 per cent for those with a negative record for enlargement. Cases with congestive failure of any type or degree (other than as an initial symptom) showed the least differential, but even among this group, 18 per cent bled, while again *only* 10 per cent among those showing no failure after the initial period developed bleeding during dicumarol therapy.

TABLE 116

Status of Bleeding and Its Relation to Dicumarol	Percentage of Cases Bleeding during Dicumarol Therapy[a] among Cases with and without Selected Pathological Conditions during the Illness[b]					
	Azotemia and/or Renal Disease		Liver Enlargement		Congestive Failure	
	Present	Not Present	Present	Not Present	Present	Not Present
Cases developing bleeding related to dicumarol	23	7	14	8	11	8
Cases developing bleeding unrelated to dicumarol	10	3	8	3	7	2
Total cases developing bleeding of any type[c]	31	10	22	10	18	10
	Number of Cases in Group					
Total cases in total sample receiving dicumarol and having known degree of reaction to dicumarol[a]	48	490	84	474	[illegible]	[illegible]

[a] Based on total ... and under suc... dicumarol (se... related to he...

[b] Any degr... classification ... cleared by the en...

[c] Two cases ha... ...unrelated to dicumarol Hence combined subgroups sometimes exceed ... total.

The physiological basis for these relationships is of interest. In the case of azotemia and/or renal disease the speed of excretion of dicumarol is obviously affected, and unless unusual care is exercised, the blood levels may accumulate unpredictably. In some types of liver enlargement, the synthesis of prothrombin may be deficient. The mechanism in the case of congestive failure is more obscure, especially since the statistical analysis reported on pages 380–381 failed to reveal any clear increase in the degree of prothrombin time reaction to dicumarol in the presence of congestive failure.

Table 116 and Appendix F, Table 59 do not include liver disease as a category since only 5 patients with liver disease received dicumarol for a sufficiently long period of time to be included in this table. The diagnosis for these 5 patients included jaundice, fatty liver, cancer of the liver, and liver disease of unspecified type. Only 1 of these 5 patients bled at all during dicumarol therapy. This one case, a patient with jaundice, vomited a small amount of guaiac positive coffee-ground vomitus on the day of death. The source of bleeding was undetermined. The other 4 cases with liver disease received the benefits of dicumarol therapy without hemorrhage.

Much of the bleeding in the other cases with positive evidence of the types described was unrelated to anticoagulants. As is apparent in Figure 120, cases developing bleeding unrelated to anticoagulants were proportionately more numerous among patients showing each of these conditions than among those free of them during the illness.

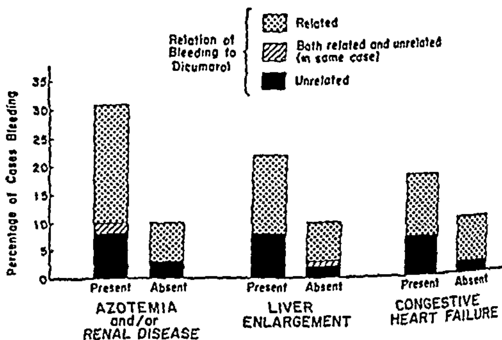


Figure 120. BLEEDING DURING DICUMAROL THERAPY IN RELATION TO SELECTED PATHOLOGICAL CONDITIONS: Percentage of cases developing bleeding related and unrelated to dicumarol during dicumarol therapy among all cases receiving dicumarol and having a known degree of reaction to dicumarol, by presence or absence of selected pathological conditions during the illness.

Increases in bleeding related to dicumarol were also apparent in all categories. The exact ratios of increase associated with these conditions probably reflect the particular diagnoses that happen to be included and may not be assumed to have general significance; however, the general results abundantly confirm the need for caution in the use of anticoagulant therapy in the presence of renal or liver dysfunction.

The experience of the majority of patients who receive dicumarol in spite of these accompanying conditions is also of medical importance. *In all categories, at least two-thirds of these patients escaped without even minor or microscopic bleeding during a period of dicumarol therapy that was continued for a sufficient period to reveal their response pattern (usually at least nine days). If such conditions had been considered absolute contraindications to any dicumarol therapy, a substantial number of patients would have been needlessly deprived of the benefits of anticoagulants.*

Bleeding without Anticoagulants

To ascertain whether this difference in bleeding in relation to these selected conditions was also characteristic of patients who were not receiving dicumarol, patients who never received any anticoagulant therapy were also classified as to the presence or absence of these conditions and whether or not they bled. The results are presented in Table 117 and Figure 121. These observations for bleeding without anticoagulants cover the total six-week period of observation whereas those for cases treated with dicumarol reported in Table 116 and Figure 120 cover only the period of dicumarol therapy, usually four weeks or less.

When this difference in the length of exposure to risk of bleeding is taken into consideration, the findings for cases never receiving anticoagulants were surprisingly close to those for unrelated bleeding in cases receiving dicumarol. Among cases with azotemia and/or renal disease who never received anticoagulants, 12 per cent bled during the six-week period of observation as compared with 4 per cent among those without these conditions. Among cases with and without the other conditions tabulated contrasts were of lesser magnitude. Seven per cent of the cases showing any liver enlargement bled during the six-week period, as compared with 4 per cent among those without this condition. The contrast was the least for congestive failure. Six per cent bled among those with congestive failure, and 5 per cent among those without congestive failure—a difference of no consequence.

Thus, even though the actual bleeding counts were low and were substantially influenced by chance, the frequency of urine examinations, and general underreporting, the consistency of the pattern of findings throughout lends confidence to the following conclusions: (1) *dicumarol must be admin-*

TABLE 117

BLEEDING WITHOUT ANTICOAGULANTS IN RELATION TO SELECTED PATHOLOGICAL CONDITIONS: Number and Percentage of Cases Never Receiving Anticoagulants Who Developed *Bleeding* Any Time during the Six-Week Period of Observation, by Presence or Absence of Selected Pathological Conditions during the Illness

Status of Pathological Condition during the Illness[a]	Cases Never Receiving Anticoagulants[b]		
	Total Cases	Cases Bleeding at Any Time during the Six-Week Period of Observation	
		Number	Per Cent
Azotemia and/or renal disease:			
Present	33	4	12
Not present	386	17	4
Liver enlargement:			
Present	82	6	7
Not present	337	15	4
Congestive failure:			
Present	124	7	6
Not present	295	14	5

[a] Defined as in footnote b, Table 116.

[b] Including treated group cases who never received anticoagulants.

The physiological basis for these relationships is of interest. In the case of azotemia and/or renal disease the speed of excretion of dicumarol is obviously affected, and unless unusual care is exercised, the blood levels may accumulate unpredictably. In some types of liver enlargement, the synthesis of prothrombin may be deficient. The mechanism in the case of congestive failure is more obscure, especially since the statistical analysis reported on pages 380–381 failed to reveal any clear increase in the degree of prothrombin time reaction to dicumarol in the presence of congestive failure.

Table 116 and Appendix F, Table 59 do not include liver disease as a category since only 5 patients with liver disease received dicumarol for a sufficiently long period of time to be included in this table. The diagnosis for these 5 patients included jaundice, fatty liver, cancer of the liver, and liver disease of unspecified type. Only 1 of these 5 patients bled at all during dicumarol therapy. This one case, a patient with jaundice, vomited a small amount of guaiac positive coffee-ground vomitus on the day of death. The source of bleeding was undetermined. The other 4 cases with liver disease received the benefits of dicumarol therapy without hemorrhage.

Much of the bleeding in the other cases with positive evidence of the types described was unrelated to anticoagulants. As is apparent in Figure 120, cases developing bleeding unrelated to anticoagulants were proportionately more numerous among patients showing each of these conditions than among those free of them during the illness.

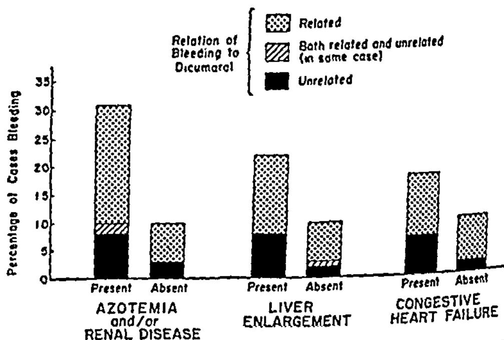


Figure 120. BLEEDING DURING DICUMAROL THERAPY IN RELATION TO SELECTED PATHOLOGICAL CONDITIONS: *Percentage of cases developing bleeding related and unrelated to dicumarol during dicumarol therapy among all cases receiving dicumarol and having a known degree of reaction to dicumarol, by presence or absence of selected pathological conditions during the illness.*

average daily dose of dicumarol was large. Except for the first and last group, for which the number of cases was too few for the computation of rates, and except for doses below 60 mg., the increase appears progressive and approximately linear. Cases receiving exceptionally small doses showed a rate in excess of that which would be expected from such a linear trend. One need not assume, however, that within this low range, increased doses do not increase the bleeding risk, for cases with lower doses may have included many recognized as presenting excessive bleeding risks. (This group would include, for example, patients given low doses because of pre-existing conditions predisposing either to bleeding or to excessive prothrombin time response)

It therefore seems reasonable to conclude that increased doses of dicumarol are associated in some manner (direct or indirect) with an increased hazard of bleeding. For any given patient this relationship is obvious since increased doses raise prothrombin levels and higher prothrombin levels bring an increased incidence of bleeding (see Figure 124, page 292). Group trends in relation to dosage are complicated, however, by the fact that patients differ greatly in the amount of dicumarol required to produce a given response. Since higher average daily doses of dicumarol are used for patients who are relatively resistant to the anticoagulant action of dicumarol, and smaller average doses for patients whose prothrombin time response indicates a relatively labile response to the drug, prothrombin time averages would not be expected to increase substantially in relation to average dosage increases. In fact, to an important degree, they did not in the computations for this study (see Table 147 and Figure 153, Chapter XII) Why, therefore, the increase in bleeding?

In the first place, the findings in regard to the relation between dosage and prothrombin times were not completely negative. The adjustment of dosage to response was clearly imperfect since *short average times* were more frequently found associated with low average doses of dicumarol than would be expected with perfect control of dosage. This is demonstrated in Table 147, Chapter XII. When accompanied by *short prothrombin times*, low average doses, although inadequate for protective purposes, would decrease the bleeding risk associated with such doses.

In addition, *occasional delayed responses* observed clinically in resistant patients

TABLE 118

BLEEDING EPISODES IN RELATION TO [illegible] Re- [illegible] of [illegible] Cases among Cases Re- [illegible]

Average Daily Dose of Dicumarol (in mg.)	Cases Receiving Dicumarol More than One Week: Number of Cases[a]	Number of Bleeding Episodes Probably Related to Dicumarol Therapy[a]	Average Number of Episodes per 100 Cases
20-39	9	—	—[b]
40-59	83	6	7.2
60-79	176	11	6.3
80-99	131	13	9.9
100-119	103	15	14.6
120-139	34	6	17.6
140 and over	7	—	—[b]
All cases receiving dicumarol more than one week.	543	51	9.4

[a] Case and episode counts exclude cases receiving dicumarol for one week or less only and cases receiving heparin but no dicumarol. Cases receiving both heparin and dicumarol are included. Episode counts exclude episodes occurring under heparin in cases receiving both heparin [illegible]

istered with particular caution in the presence of azotemia or renal disease, (2) some increased watchfulness is also appropriate when liver enlargement or congestive failure are present, and (3) since some increase in the incidence of bleeding in the presence of these conditions was found even without anticoagulants, anticoagulant therapy cannot be considered responsible for all the bleeding that occurs during such treatment.

BLEEDING IN RELATION TO PROCEDURES IN ADMINISTRATION OF ANTICOAGULANTS

Bleeding under anticoagulants differs not only in relation to the medical condition of the patient but also in reaction to the procedures used in therapy, such as dosage, length of therapy and prothrombin levels. Each of these influences was also analyzed statistically.

Episodes of Bleeding in Relation to the Average Daily Dose of Dicumarol

The relation of dicumarol dose to bleeding was not as direct and simple as one would suppose *a priori* since individual reactions differ greatly. Five hundred and forty-three cases in this study received dicumarol for a period of more than one week. Among these cases 51 episodes of bleeding occurred which were probably related to dicumarol therapy, an incidence of 9.4 episodes of bleeding per 100 cases so treated. These cases were separated into groups according to the average daily dose of dicumarol received. The number of episodes of bleeding per 100 cases was then calculated for each increment of 20 mg. in the average daily dose of dicumarol These data are summarized in Table 118 and shown graphically in Figure 122.

The number of episodes of bleeding per 100 cases was in general greater when the

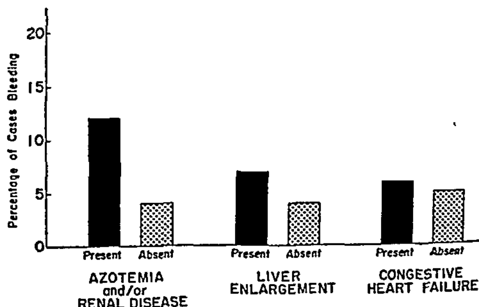


Figure 121. BLEEDING IN CASES RECEIVING NO ANTICOAGULANTS IN RELATION TO SELECTED PATHOLOGICAL CONDITIONS: Percentage of cases never receiving anticoagulants who developed bleeding any time during the six-week period of observation, by presence or absence of selected pathological conditions during the illness.

bleeding in resistant patients given high doses of dicumarol.

Episodes of Bleeding in Relation to the Duration of Dicumarol Therapy

It has been suggested that the prolonged administration of dicumarol in amounts consistent with clinical practice might lead to bleeding whereas the administration of similar amounts of the drug for relatively short periods of time would have no such effect Such bleeding, if confirmed, might perhaps represent an effect of the drug other than its usual anticoagulant action, for example, a direct effect on the blood vessels themselves, or damage to the hepatic parenchyma. Of interest in this connection are the experimental studies of Rose, Harris and Chen,[204] Wakim, Chen and Gatch,[237] Richards and Cortell,[200] Roderick,[202] McCarter, Bingham and Meyer,[145] Bollman and Preston,[30] Irish and Jaques,[99] Ham and Curtis,[79] and Jansen [100] The findings of these studies are summarized in Marple and Wright,[232] pages 142–144.

The comparatively brief period of time for which dicumarol was administered to patients observed in this study does not permit any conclusion to be drawn as to the possible hemorrhagic effect of the drug if administered for months or years. Parenthetically, however, one may remark that there is no evidence to support the view that the administration of dicumarol for periods of months or even years will produce any additional hemorrhagic tendency or renal, or liver damage The reports of Quick[184] Prandoni and Wright[190, 234] and Aggeler[1] are pertinent in this connection. The clinical use of dicumarol on a "long-term" basis in increasing numbers of patients has also so far failed to support such a possibility. Successful experience with long-term therapy has been reported by Wright and Foley,[45, 231] by Sprague and Jacobsen,[227] and by Nichol and Borg [163]

The data obtained in this study do indicate the influence of dicumarol on bleeding episodes occurring week by week during the administration of the drug for a total period of six weeks. With the exception of the relatively small number of patients being treated the world over with "long-term" therapy, this period certainly represents the usual limit of time for which anticoagulant therapy is being used in current medical practice.

To study the relation of bleeding to the duration of therapy, each new bleeding episode probably related to dicumarol therapy was classified according to the day of dicumarol therapy on which it began. Rates per 1000 days of such therapy were then calculated for each week of dicumarol administration, the first day of dicumarol being used in this instance as the starting point. The results, as shown in Table 119 and, graphically, in Figure 123, were, week by week, as follows: 3.4, 3.7, 4.2, 3.6, 1.0, and 1 7. These figures are closely similar for the first four weeks. They reach a peak during the third week, but fall off abruptly after the fourth week. The meaning of these fluctuations is not clear. Rates after the fourth week were particularly unreliable because relatively few patients were treated for long periods and those that were may have been continued partly because of their below-average bleeding record. It should be emphasized also that these rates relate to the day of onset of bleeding and not to the total days of bleeding in each period. How data on prevalence of bleeding at given periods of the illness (based on data on duration of episodes) would have differed from the present findings is not known and could not be investigated [illegible] ade[illegible]

T[illegible] and [illegible] wer[illegible] examined separately. Those due to dicumarol therapy began on the average after 17 days of dicumarol therapy. Such episodes reached a peak during the third week, when they contributed all but

given high doses to counteract a slow initial response to dicumarol are probably a factor. Such delayed prolongations would involve a marked increase in bleeding risk to the individual that would be quite disproportionate to the relatively small influence of these high times on the general prothrombin time averages as computed.[a] Their influence would, therefore, be more evident in dosage related to bleeding rates than in dosage related to prothrombin time averages.

The foregoing interpretation of increased bleeding risk associated with high dosage levels in terms of related changes in prothrombin times rather than in terms of some obscure direct influence of dicumarol on bleeding that is independent of prothrombin levels is lent credence by the fact that the percentage of bleeding incidents beginning at times of 50 seconds or more (7 per cent or less) increased as dosage levels increased. For the dosage categories in Figure 122, these percentages were in sequence from the lowest dosage group (40-59 mg.) upward as follows: 17, 27, 31, 47, and 50 per cent. Elimination from the rates of episodes occurring at times of 50 seconds or more reduces the upward trend shown in Figure 122 nearly to a horizontal. Conclusive proof of the above interpretation would require day rates similar to those in Table 120, page 291 for each dosage level, a complicated procedure which the size of the sample does not justify. Nevertheless, the available observations are more consistent with the interpretation that the relation of dosage to bleeding is indirect and operates through the effect of the drug on prothrombin time than with the interpretation that its influence is in some manner independent of prothrombin levels. *For the practicing physician, the findings serve merely to emphasize the need for special care in the observation of prothrombin times and for watchfulness for*

[a] The method of computing provided for an arbitrary reduction in the influence of times over 60 seconds. See footnote f of Appendix F, Table 79.

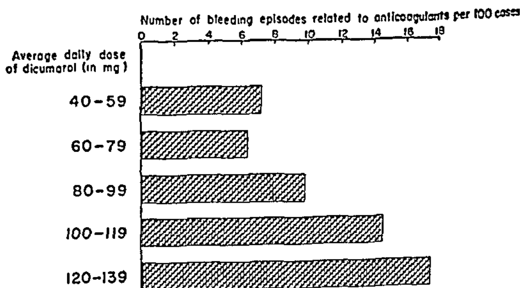


Figure 122. BLEEDING EPISODES BY AVERAGE DICUMAROL DOSAGE: Average number of bleeding episodes probably related to dicumarol therapy per hundred cases in the total sample receiving dicumarol more than one week and receiving average daily doses of various amounts.

bleeding related to dicumarol is, by these data, distinctly reduced after the fourth week, largely as a result of the absence of episodes of bleeding aggravated by dicumarol, but selection of patients with minimal bleeding risk for continued therapy or better control of prothrombin levels may well explain the decline.

Episodes of Bleeding in Relation to Prothrombin Levels

There is generally a closer relationship between the incidence of bleeding episodes and the prothrombin concentration (degree to which the prothrombin time is prolonged and, conversely, the degree to which the prothrombin activity is reduced) than that between the incidence of bleeding episodes and the dosage of dicumarol. The prothrombin level is an indication of the *response* of the patient to the anticoagulant action of dicumarol irrespective of the dose or doses of dicumarol administered. Different patients react differently to any given dose of dicumarol; the only method which is known to give an estimate of this reaction is the determination of the prothrombin time. The results obtained by such a determination may be expressed directly in seconds (prothrombin time), or may be converted into the degree by which the prothrombin activity is reduced (expressed in percentage of normal prothrombin activity) according to a suitably constructed hyperbolic curve.

Episodes of bleeding occur most frequently when the prothrombin time is prolonged excessively (when the prothrombin activity is greatly reduced), but episodes of bleeding also occur, often unpredictably, when the prothrombin time is prolonged only slightly above normal. Thus, episodes of bleeding may occur not only when the prothrombin time is prolonged to, or beyond, the therapeutic range, but may occur even when the prothrombin time has not been

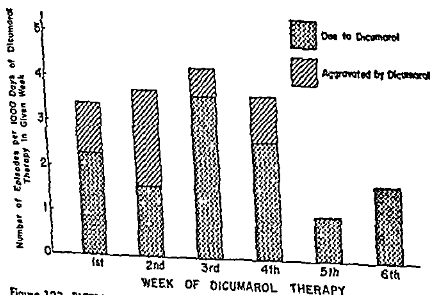


Figure 123. BLEEDING EPISODES BY DURATION OF DICUMAROL THERAPY: Average number of bleeding episodes in the *total sample due to, or aggravated by,* dicumarol therapy beginning after various periods of dicumarol therapy per thousand days of dicumarol therapy *during similar periods.*

0.6 to the total rate. A peak at this time is probably the natural result of the tendency on the part of physicians to begin anticoagulant therapy with conservative doses and then to increase the dose for patients who are slow in responding. Such a peak is also consistent with the fact that the proportion of prothrombin times during therapy that were 50 seconds or more reached a maximum in the third week of the illness (see Appendix F, Table 77).[c]

Episodes aggravated by dicumarol occurred on the whole earlier than those due to dicumarol. On the average they began after 13 days of dicumarol therapy and on a rate basis reached a peak *during the second* week. In the present series new episodes of this type did not occur at all after the fourth week. In fact, such episodes were consistently low except during the second week, when they contributed more than half of the total rate.

These data indicate that the hazard of bleeding due to, or aggravated by, dicumarol does not increase with the duration of such therapy over a period of six weeks. The total hazard from bleeding does appear to increase slightly week by week through the first three weeks but this increase can be explained on the basis of increases in prothrombin time levels. *One may conclude further that if a pre-existing bleeding tendency is to be aggravated or precipitated by the administration of dicumarol, this effect will usually be evident by the end of the second week. If bleeding occurs as a result of dicumarol, it is most apt to appear before the end of the third or fourth week.* The hazard of new episodes of

[c] Comparison is approximate only since prothrombin time data cited were by week of illness and rates under discussion were computed on the basis of week of dicumarol therapy. Dicumarol therapy for the treated group was begun on the average on the fifth day.

TABLE 119

BLEEDING EPISODES BY DURATION OF DICUMAROL THERAPY: Number of Bleeding Episodes Related to Dicumarol Therapy Occurring in Patients Who, at the Time the Episode Began, Had Received Dicumarol for Various Periods of Time and Number of Such Episodes per Thousand Days of Dicumarol Therapy Given during Corresponding Periods of Therapy

Day of Dicumarol Therapy (1st day = 1st day patient received dicumarol)	Number of Days of Dicumarol Therapy Given during Period[a]	Bleeding Episodes Probably Related to Dicumarol Therapy[b]					
		Number of Episodes			Average Number of Episodes per 1000 Days of Dicumarol Therapy in Corresponding Period		
		All Episodes Related to Dicumarol	Episodes Probably Due to Dicumarol	Episodes Probably Aggravated by Dicumarol	All Episodes Related to Dicumarol	Episodes Probably Due to Dicumarol	Episodes Probably Aggravated by Dicumarol
1st -7th	3,863	13	9	4	3.4[c]	2.3	1.1
8th -14th	3,747	14	6	8	3.7	1.6	2.1
15th -21st	3,583	15	13	2	4.2	3.6	.6
22nd-28th	3,040	11	8	3	3.6	2.6	1.0
29th -35th	1,960	2	2	.	1.0	1.0	0.0
36th -42nd	573	1	1	..	1.7	1.7	0.0
Total, all days.. .	16,766	56	39	17	3.3	2.3	1.0

[a] *Counts include control group patients when under dicumarol but exclude days when heparin was received.*

[b] Counts include bleeding episodes developing in occasional control patients receiving dicumarol under special circumstances, as well as those occurring in the treated group, but exclude episodes occurring when the patient was receiving any heparin. As a result, total counts differ from those cited in other hemorrhage tables.

[c] Bleeding due to dicumarol was higher from the 4th to the 7th da ... during the first 3 days, whereas the reverse was true of bleeding episodes only agg

bleeding related to dicumarol is, by these data, distinctly reduced after the fourth week, largely as a result of the absence of episodes of bleeding aggravated by dicumarol, but selection of patients with minimal bleeding risk for continued therapy or better control of prothrombin levels may well explain the decline.

Episodes of Bleeding in Relation to Prothrombin Levels

There is generally a closer relationship between the incidence of bleeding episodes and the [illegible]

prothrombin activity is reduced) than that between the incidence of bleeding episodes and the dosage of dicumarol. The prothrombin level is an indication of the response of the patient to the anticoagulant action of dicumarol irrespective of the dose or doses of dicumarol administered. Different patients react differently to any given dose of dicumarol; the only method which is known to give an estimate of this reaction is the determination of the prothrombin time. The results obtained by such a determination may be expressed directly in seconds (prothrombin time), or may be converted into the degree by which the prothrombin activity is reduced (expressed in percentage of normal prothrombin activity) according to a suitably constructed hyperbolic curve.

Episodes of bleeding occur most frequently when the prothrombin time is prolonged excessively (when the prothrombin activity is greatly reduced), but episodes of bleeding also occur, often unpredictably, when the prothrombin time is prolonged only slightly above normal. Thus, episodes of bleeding may occur not only when the prothrombin time is prolonged to, or beyond, the therapeutic range, but may occur even when the prothrombin time has not been

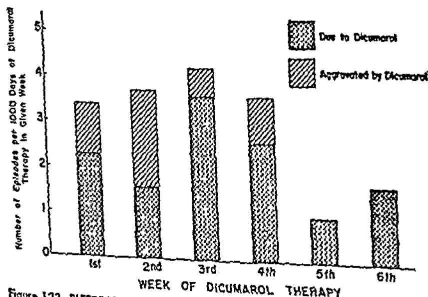


Figure 123. BLEEDING EPISODES BY DURATION OF DICUMAROL THERAPY: Average number of bleeding episodes in the total sample due to, or aggravated by, dicumarol therapy beginning after various periods of dicumarol therapy per thousand days of dicumarol therapy during similar periods.

prolonged sufficiently to interfere with the occurrence of thromboembolic phenomena. The presence of a pre-existing lesion which is a potential source of bleeding such as a gastrointestinal ulcer or cancer which predisposes the patient to bleeding explains some, but not all, of these episodes of bleeding which occur at relatively small prolongations of the prothrombin time. In any instance of such bleeding, a search should be made for pre-existing causes such as open ulcers or wounds, malignant tumors or blood dyscrasias, pre-existing hypoprothrombinemia, disease of the kidneys or liver, etc.

In all instances in which dicumarol is administered, the prothrombin time should be determined before the first dose is given, or at least within 20 hours before an important effect on the prothrombin time can be found, and daily thereafter until the response of the patient to given doses of the drug is well known. If at any time the prothrombin time is excessively prolonged beyond normal expectation, the test should be repeated promptly. If the excessive prolongation is confirmed, the drug should be withheld and, possibly, specific active measures invoked to antagonize the anticoagulant action.

Total Bleeding Counts by Prothrombin Levels

In the present study the 56 bleeding episodes related to dicumarol[b] were tabulated according to the highest reported prothrombin time for the day the episodes began or the preceding day, whichever was the highest. It was believed that this procedure would reflect most accurately the influence of prothrombin time on the occurrence of bleeding related to dicumarol since such bleeding was believed to follow rather than precede, or even accompany, a sudden prolongation of prothrombin time. Counts on this basis are presented in the first three columns of Table 120. Counts exclude both episodes unrelated to anticoagulants but occurring during dicumarol therapy and episodes at times when patients were receiving no dicumarol.

Eighteen, or about a third (32 per cent), of all related episodes thus classified occurred when the longest prothrombin time on either the initial day or the day previous was less than 30 seconds (17 to 100 per cent prothrombin activity). An additional 11 episodes (20 per cent of the total) occurred when times were between 30 and 39 seconds (11 to 16 per cent prothrombin activity). Since the therapeutic range advocated to the participants in this study included a range of prothrombin activity of from 10 to 30 per cent, it is apparent that more than half (52 per cent) of all bleeding episodes occurred when times did not exceed this recommended range.

This result may at first appear to contradict expectations, but it must not be forgotten that patients were maintained at such times for most of their periods of therapy with consequent disproportionate increase in the opportunity for bleeding at these times. In fact, 86 per cent of the known prothrombin times during dicumarol therapy were below 40 seconds.

The remaining 27 bleeding episodes related to dicumarol began on days when the time for that day or the day preceding was 40 seconds or more (10 per cent or less prothrombin activity). Of these, 11 occurred at times of 60 seconds or more (6 per cent or less) and the other 16 were equally divided between 40 to 49 seconds (10 to 8 per cent) and 50 to 59 seconds (7 per cent). Because of the small number of days patients were maintained at these excessively prolonged times, the counts shown without reference to the base exposure period greatly understate the bleeding risk involved in high prothrombin times.

In Table 120, Columns 2 and 3, episodes due to dicumarol are reported separately from episodes aggravated by dicumarol. It would seem medically reasonable to expect that patients with pre-existing conditions conducive to bleeding would bleed

[b] *Three bleeding episodes occurring under heparin were excluded.*

sooner and at shorter prothrombin times than those without such conditions, and similarly that they would be more sensitive to excessively high times. The reported distributions, in which episodes aggravated by dicumarol were more frequent in the lowest and highest prothrombin time ranges than in the intermediate ones, are consistent with this supposition. In view of the small numbers involved, however, little reliance should be placed on these details of the reported distributions.

Bleeding Counts Related to Patient-Days at Various Levels

For a true comprehension of the relation of bleeding to prothrombin times, the counts must be converted to rates showing the incidence of bleeding per 1000 days of therapy at given prothrombin times. Rates of this type are shown in the last column (column 6) of Table 120 and in Figure 124. Since patient-days of therapy were never counted in terms of times classified according to whichever time in a two-day sequence was the more prolonged, bleeding *counts*, to be comparable with available day counts, had to be stated in terms of the prothrombin time the day the episode began, rather than as in the preceding discussion in terms of the higher of two days. The recounting of the episodes in this manner (see column 4 of Table 120) lowers the number of episodes reported for prolonged times and increases the number for short times. This procedure probably understates the role of prolonged times in the production of bleeding since some types of episodes, such as melena, may

TABLE 120

[illegible]

In Seconds	In Per Cent Prothrombin Activity	All Episodes Related to Dicumarol (Col. 1)	Episodes Due to Dicumarol (Col. 2)	Episodes Probably Aggravated by Dicumarol (Col. 3)	[illegible]gan—All Related Episodes (counts used for rates quoted) (Col. 4)	[illegible] at Given Levels (Col. 5)	[illegible] at Given Prothrombin Levels (Col. 6) (equals Col. 4 ÷ Col. 5)
Under 30	16 8% or over	18	11	7	21	8,024	2.6
30-33	18.7 -10.9	11	9	2	12	3,162	3.8
40-49	10.8 - 7 84	8	6	2	8	1,092	7.3
50-59	7 83- 6 30	8	6	2	7	408	17.2
60 and over	6 29 and under	11	7	4	7	337	20.8
Total episodes related to dicumarol		56	39	17	56[d]	13,023	4.3

[a] For method of conversion, see pp. 350–352. Times cited refer [illegible]

[b] When no proth[illegible] estimated from p[illegible] those cited in oth[illegible] therapy in contr[illegible] ceiving heparin a[illegible]

[c] Counts not u[illegible] [illegible] of counts of patient-days of exposure done by same two-day sequence procedure needed for correct base for such a rate.

[d] Total includes one bleeding episode at an unknown prothrombin level, the time for which could not be estimated. Hence total exceeds sum of components shown.

be explained more adequately on the basis of the record the preceding day than in terms of the time on the day melena was observed.

Even with this understatement, however, the rates reported in column 6 of Table 120 show that the risk of bleeding begins to increase as times exceed 40 seconds (below 11 per cent) and increases rapidly as times reach 50 seconds (7 per cent) and 60 seconds (6 per cent). The difference between the rate for 25–39 seconds and the combined rate for 40–49 seconds and 50 seconds and over is very striking and can hardly be attributed to chance. Clearly (1) the *substantial proportion of the total bleeding* episodes related to anticoagulants that began at times below 30 and 40 seconds is the result of the large number of days that patients were maintained at these levels and not to any inherently high bleeding risk associated with these customary levels, and (2) *the failure to control prothrombin times in such a manner as to eliminate times above 40 or at most 50 seconds (i.e., times of 7 per cent or less) involves an excessive bleeding risk.*

Simultaneous consideration of these findings and those for the incidence of thromboembolic complications at various prothrombin times makes possible an inductive working definition of the therapeutic range for prothrombin times during anticoagulant therapy. *Such a definition is attempted in* Chapter XII. This chapter also explains in more detail the principles and procedures involved in securing the rates shown in Table 120 and in Figure 124.

Treatment of Episodes of Bleeding

Continuation or Discontinuation of Anticoagulants

The first step in the management of excessive hypoprothrombinemia, or of hemorrhage due to dicumarol, or of excessive

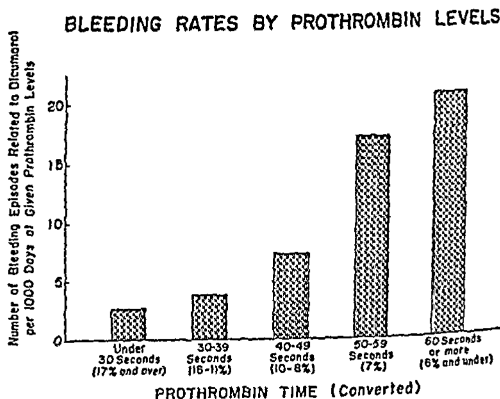


Figure 124. BLEEDING RATES BY PROTHROMBIN LEVELS: *Average number of bleeding episodes related to dicumarol therapy per thousand days at various prothrombin levels from the second day of dicumarol therapy through four days after the last dose for all patients in the total sample receiving dicumarol.*

prolongation of the clotting time, or of hemorrhage due to heparin is ordinarily the discontinuation, temporarily or perma- -ently as circumstances warrant, of the use f anticoagulants. The decision whether or ot to discontinue anticoagulant therapy vill be guided by two considerations: the eriousness of the bleeding episode or the legree to which the prothrombin time or clotting time is prolonged and the urgency of the situation for which anticoagulant therapy is being administered.

Where bleeding is serious, or where the hazard of bleeding is felt to outweigh the advantage of continued anticoagulant therapy, the anticoagulant should be withheld immediately. Specific measures intended to prevent or to ameliorate bleeding may be instituted if felt desirable or necessary. When the threat of hemorrhage is removed, consideration may then be given to the desirability of reinstituting anticoagulant therapy.

In instances where thromboembolic episodes appear imminent or constitute a serious hazard *to the patient*, as for example, following repeated pulmonary embolism, or progressive iliofemoral thrombophlebitis, it may be considered necessary to maintain anticoagulant therapy despite bleeding or the threat of bleeding. *In such* circumstances the attending physician is faced with a delicate decision in which the continuation of anticoagulant therapy represents a calculated risk.

Ordinarily [illegible] me [illegible] the [illegible] wit [illegible] anticoagulants themselves, at least temporarily. This is particularly true if bleeding is serious, or if the *pro*thrombin or clotting times are seriously prolonged.

Table 121 and Figure 125 analyze the extent to which such measures were invoked in the present study. For this purpose all episodes in both the control and treated groups are combined. On the whole, action in the case of episodes related to anticoagulants was more vigorous than in the case of unrelated episodes. For example, half of the unrelated episodes occurring during anticoagulant therapy were left untreated and anticoagulant therapy was not interrupted, whereas for only a third (37 per cent) of related episodes, neither action was taken. Obviously such episodes could not have been of any very great significance. Similarly, specific measures to antagonize the effects of anticoagulants were more frequently applied in the case of episodes with some relation to anticoagulant therapy. Only 5 per cent of the bleeding episodes occurring when no anticoagulants were in effect received specific treatment. One third of those occurring during anticoagulant therapy but unrelated to such therapy received specific countermeasures, while nearly half (45 per cent) of those episodes due to, or aggravated by, anticoagulants received treatment to antagonize the anticoagulant effect. These specific measures are discussed in the following section.

Treatment of bleeding was usually conservative. Specific measures to antagonize the anticoagulant effect were invoked in many instances of mild or moderate bleeding. The purpose of these measures was more often to prevent serious bleeding than to cope with it. Anticoagulants were discontinued in less than half of related episodes treated with specific countermeasures—again an indication of the mildness of these episodes.

Specific Therapy to Antagonize Anticoagulant Effect

Excessive hypoprothrombinemia or hemorrhage due to dicumarol therapy usually responds promptly *to* transfusions with fresh whole blood or plasma in amounts of 300–500 cc. The effect of such a transfusion is often temporary, however, and the prothrombin time is found after a period of several hours to be prolonged once again. For this reason, if transfusions of blood or

plasma are alone to be used in the treatment of hypoprothrombinemia or bleeding from dicumarol therapy, they must frequently be given *repeatedly over a period of several days. It is important that whole blood or plasma used for this purpose be fresh, though it may be citrated, since stored blood (bank blood) is often ineffectual in either halting bleeding or in restoring a prolonged prothrombin time to normal.*

It has been demonstrated repeatedly both in animal experiments and in clinical practice that most instances of excessive hypoprothrombinemia or bleeding due to dicumarol can be corrected by the adminstration of preparations exhibiting vitamin K activity *if these are given parenterally in sufficient doses.*[171] The synthetic naphthoquinones are effective when they are given intravenously in doses of approximately 75 mg., but such doses should be repeated at intervals of every four hours until bleeding has ceased and the prothrombin time has returned to, and been maintained at, approximately normal. Even then, the prothrombin time should be determined periodically for several days lest it again be prolonged and bleeding occur. Vitamin K_1 has been effective in instances when the synthetic naphthoquinones have failed to produce a satisfactory response. It may be given orally in doses of 250–500 mg. with prompt effective results. Vitamin K_1 oxide was not used therapeutically in any of the patients in this study since this information has developed in the main since the completion of the case reports for this study. Repeated doses and even single doses of vitamin K_1 preparations totalling from 500 to 1000 mg. have been given clinically without apparent ill-effect. Recently, doses of Vitamin K_1 as low as 10–50 mg. have been found to be effective in most cases. These small doses have the advantage of reducing the

TABLE 121

EXTENT OF TREATMENT OF BLEEDING EPISODES: Number and Percentage of Bleeding Episodes in the Total Sample in Which Various Types of Action Were Taken with Respect to Discontinuance of Anticoagulants and Specific Therapy to Antagonize the Anticoagulant Effect, by Relation of Episode to Anticoagulant Therapy

Action Regarding Specific Therapy and Continuation of Anticoagulant Therapy	Episodes Probably Unrelated to Anticoagulant Therapy				Episodes Due to, or Aggravated by, [illegible]	
	[illegible]		[illegible]			
	Number	Per Cent of Total	Number	Per Cent of Total	Number	Per Cent of Total
No specific therapy:						
Anticoagulants continued	—	—	12	50	22	37
Anticoagulants discontinued	—	—	4	17	10	17
Anticogulants not in effect at time of onset	36	95	—	—	—	—
Some specific therapy:[a]						
Anticoagulants continued	—	—	4	17	15	25
Anticoagulants discontinued	—	—	4	17	12	20
Anticoagulants not in effect at time of onset	2	5	—	—	—	—
Total episodes (in total sample)	38[b]	100	24[b]	100	59[b]	100

[a] For details as to types of treatment, see pp. 293–296

[b] Total for related episodes includes 5 episodes in the control group related to anticoagulants omitted from most other tabulations Other totals also differ from those elsewhere reported since they include both the control and treated groups, both classified by relation to anticoagulants.

prothrombin time without maintaining a prolonged action of many days which would interfere with the renewal of anticoagulant therapy.

We have previously advised that "When the prothrombin clotting time of patients receiving dicumarol becomes excessively prolonged (when the prothrombin activity is reduced to 10 per cent or less of normal), 30 to 60 mg of menadione bisulfite may be given intravenously and subsequent doses of dicumarol omitted or reduced in amount. If bleeding of a significant degree occurs, 60–72 mg. of menadione bisulfite may be given intravenously and followed immediately by a transfusion of 500 cc. whole fresh blood. Transfusions may be given periodically to control bleeding and to combat any anemia which develops."[a] The diagnosis and treatment of cardiac tamponade, an occasional complication of anticoagulant therapy, is discussed on page 429.

Vitamin K preparations are not indicated if the patient is under heparin as the sole anticoagulant and the prothrombin time is not prolonged. Hemorrhages occurring when the patient is receiving heparin only should be treated by discontinuing heparin and giving, if necessary, fresh whole blood transfusions. Protamine sulfate has also been recommended for such emergencies but has not been widely used.

In the present study a total of 37 bleeding episodes received specific therapy of some

[a] Quoted from Marple and Wright,[13] p. 164.

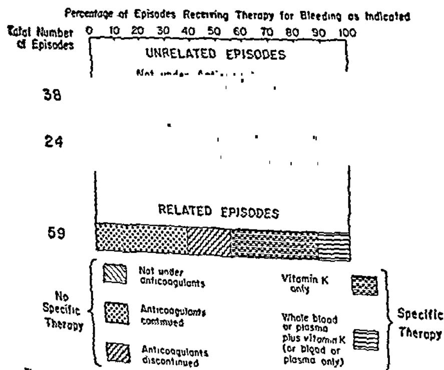


Figure 125. TREATMENT OF BLEEDING EPISODES- Percentage of bleeding episodes in the total sample in which various types of action were taken with respect to discontinuance of anticoagulants and specific therapy to antagonize the anticoagulant effect, by relation of episode to anticoagulant therapy.

type (with or without discontinuance of anticoagulants). Water-soluble vitamin K without supplementation with blood or plasma was the most frequent type of therapy and was used for 25, or 68 per cent, of the episodes requiring treatment. This therapy was also used in conjunction with fresh blood or plasma in the treatment of another 9 episodes, or 24 per cent of the total. Only 3 episodes (8 per cent) were treated with fresh blood or plasma without vitamin K. Totals for component groups are too small to permit meaningful comparisons of the therapy methods used for episodes related and unrelated to anticoagulants.[f] *When specific therapy for bleeding was needed, chief reliance was placed on water-soluble vitamin K. It is probable that this reflects both the relative absence of serious bleeding encountered in the cases observed and the general effectiveness of this countermeasure.*

SUMMARY

All evidences of bleeding reported observed clinically (including laboratory findings) among both treated and control cases were reviewed and counted no matter how minor[a] and regardless of whether they had been defined by the attending physician as hemorrhagic episodes. The definitions applied were exceptionally strict (pages 257–258) and led to the inclusion of a number of episodes that were never diagnosed as hemorrhagic complications by the attending physician. Analysis by these procedures led to the following major findings:

1. Some evidence of bleeding was observed clinically among 5.2 per cent of the control group during the period of observation and among 12.9 per cent of the treated group. Actual bleeding episodes of all types by the very strict definitions adopted numbered 5.9 per 100 cases in the control group and 15.3 per 100 cases in the treated group. Both differences are highly significant statistically.

2. Three cases in the control group (0.7 per cent) and 12 cases in the treated group (2.0 per cent) bled more than once during the period of observation.

3. Bleeding episodes due to, or aggravated by, anticoagulants were observed clinically in 7.8 per cent of the treated group cases and numbered in total 9.2 episodes per 100 cases, or 3.3 per 1000 days of anticoagulant therapy given.

4. Episodes of bleeding occurred in the absence of anticoagulant therapy or under therapy but due entirely to other causes. Such episodes observed clinically numbered 1.6 per 1000 days of observation in both the control and treated groups and were approximately similar in severity. The two groups were therefore considered about equivalent in inherent bleeding risk.

5. More than half (54 per cent) of the bleeding episodes in the treated group related to anticoagulants were of mild severity and an additional two-fifths (39 per cent) were moderate in severity. Only 4 episodes (7 per cent) were severe among 577 treated group patients receiving anticoagulants for a total of 16,208 days. In only 1 of these 4 severe episodes were anticoagulants clearly the sole factor in the development of bleeding. None observed clinically was fatal. (For data on fatal hemorrhages diagnosed at autopsy, see Chapter XIII.)

6. Microscopic hematuria was the most

[f] Of the 8 bleeding episodes occurring under anticoagulants but unrelated to it that received specific therapy, 5 were treated with vitamin K only; 2, with vitamin K plus blood or plasma; and 1, with fresh blood only. Of the 27 episodes due to, or aggravated by, anticoagulants that received specific therapy, 20 were treated with vitamin K only; 6, with fresh blood and/or plasma plus vitamin K; and 1, with fresh blood only. Of the 2 episodes that occurred when no anticoagulants were being given that received treatment, 1 was treated with fresh blood only and the other, with fresh blood plus vitamin K. These data appear visually in percentage form in Figure 125.

[a] A few inconsequential observations were excluded. See discussion in footnote d, pp. 259-260.

frequent form of bleeding related to anticoagulants in the treated group and constituted about two-fifths of the total. Gross hematuria, hematemesis, melena, epistaxis, and hemoptysis were the chief other types observed.

7. In less than half of the episodes related to anticoagulants did the attending physician believe the episode warranted treatment to antagonize the anticoagulant effect. More than a third were so mild that (in addition to being left untreated) anticoagulants were not even discontinued when the bleeding developed. A number were not even recognized as bleeding in the attending physician's report on the case.

8. In the therapy of bleeding episodes chief reliance was placed on water-soluble vitamin K. In a minority of cases this type of vitamin K was supplemented by fresh blood or plasma. Vitamin K_1 or K_1 oxide was not readily available at the time this study was in progress.

9. Patients with complicating azotemia or renal disease bled more frequently during dicumarol therapy than did those without these conditions. To a lesser extent this was also true of patients with liver enlargement or congestive failure. In addition, the much larger group of patients classified as generally poor risk cases developed a slightly higher average number of bleeding episodes per 100 cases than did good risk treated cases. Even among these various handicapped groups, however, more than two-thirds of each type studied escaped entirely without bleeding during dicumarol therapy. Examination of bleeding among cases receiving no anticoagulants revealed that bleeding was also increased in these conditions even in the absence of anticoagulant therapy.

10. The incidence of bleeding showed no consistent trend in relation to the age of the patient.

11. New episodes of bleeding related to anticoagulants continued to be observed throughout the six-week period at a fairly constant rate (when stated in terms of number per 1000 days of anticoagulant therapy).

12. Bleeding episodes unrelated to anticoagulants were most frequent in the first two weeks of the illness and were minimal thereafter.

[illegible] the incidence of [illegible] was interpreted as due to the effect of dicumarol on the prothrombin time.

14. After the initial period of treatment, bleeding related to anticoagulants showed no tendency to increase with increases in the duration of dicumarol therapy. Episodes aggravated by dicumarol showed a peak in the second week of dicumarol administration and episodes due to anticoagulants, a peak in the third week.

15. The percentage of cases in the treated group in the present study who showed any bleeding (12.9 per cent) was higher than the pooled percentage for 12 other controlled studies of anticoagulant therapy in myocardial infarction (6.3 per cent). This difference probably reflects the relatively full reporting of minor evidences of bleeding in the present study. *In contrast to the general figure, the percentage showing severe bleeding (0.8 per cent) in the treated group of the present study was close to the pooled figure for 10 other controlled studies (0.6 per cent).*

On the basis of these findings as summarized, one may conclude that (1) anticoagulants increase the risk of hemorrhage, and (2) when control procedures are adequate, this increase is sufficiently slight and the episodes of bleeding sufficiently mild, so that the benefits of anticoagulants greatly overbalance the accompanying risk of hemorrhage. Further analysis of the hemorrhagic findings is given in Chapter XIII which deals with the observations at autopsy.

CHAPTER X

Thromboembolic and Hemorrhagic Complications under Heparin

INTRODUCTION

HEPARIN was the first practical anticoagulant to be used regularly in both experimental and clinical work. Reasonably purified preparations were isolated as early as 1922 by Howell at Johns Hopkins and at least one of these was made commercially available in the same year. However, purification of these early preparations was not complete and their usefulness was limited by the frequent and sometimes serious side reactions which accompanied their administration. Heparin was studied intensively in the laboratories of C. H. Best in Toronto[30] and of J. E. Jorpes in Stockholm during the nineteen thirties and a considerable clinical experience was gained during this decade. In 1939, Jorpes published his classic monograph on the use of heparin in the treatment of thrombosis.[103] Even when highly purified preparations of heparin became available and side reactions were thus practically eliminated, heparin suffered the serious disadvantages of being exceedingly expensive and of requiring parenteral administration to be effective.

With the discovery of 3,3′ methylenebis-(4-hydroxycoumarin) (dicumarol) and the elucidation of its chemistry and pharmacological action by Link and his associates,[120] heparin was discarded by many workers in favor of the new, inexpensive and orally-effective anticoagulant. However, the delay of from 48 to 72 hours in the effective anticoagulant action of dicumarol following its initial administration was promptly recognized to be a serious disadvantage in those instances where immediate effective anticoagulant action was imperative, e.g., following acute thrombosis. At the time this study was initiated, the suggestion had already been made that heparin and dicumarol should be administered concurrently at the outset when an immediate anticoagulant effect was deemed necessary. Heparin would then be continued only until dicumarol had produced an effective degree of anticoagulant action (until a satisfactory prolongation of the prothrombin time had been attained), whereupon heparin could be discontinued and the patient maintained on dicumarol. It was in the hope of obtaining significant information on the effectiveness of this "combined therapy" that the responsible investigators were privileged to utilize it at their discretion. Unfortunately, as this chapter indicates, the use of heparin was limited to an extent which precluded full statistical evaluation of the method.

Combined therapy is still recommended in those instances where an immediate anticoagulant effect is essential.[122, 157, 238] The discovery of new coumarins or compounds which have a coumarin-like action and which produce an effective anticoagulant action more promptly than does dicumarol may eventually make combined therapy unnecessary, but experience with the presently available compounds (Tromexan, cumopyran, phenylindanedione) has not, as yet, disclosed a completely effective substitute for heparin-coumarin therapy in such instances.

In the present series, heparin was the only anticoagulant other than dicumarol used in the treatment of patients. Its use with odd-day cases was governed entirely

by the discretion of the attending physician although methods of administration were suggested by the Central Laboratory. In actual practice, relatively little use was made of heparin. In other chapters of this report the effects of heparin are either buried in totals relating primarily to dicumarol or events occurring during heparin therapy are omitted in counts in the interest of clarifying other relationships. Clinical experience with heparin in coronary thrombosis is similarly scattered and seldom brought together statistically. For these reasons, it was decided that a review specifically of the experience with heparin in this series, particularly as it related to complications and hemorrhages, would assist in the evaluation of this anticoagulant as a therapeutic supplement to dicumarol in the treatment of myocardial infarction.

METHODS OF ADMINISTERING HEPARIN

One hundred and fifteen cases in this study, or 19 per cent of the cases treated with anticoagulants, were given heparin. These cases were all treated in eleven of the hospitals participating in the study. No cases were treated with heparin in the other 5 cooperating hospitals. Among the 11 hospitals using heparin, the majority administered it to patients in this series in not more than 4 instances. Four hospitals administered heparin to more than 4 cases each, namely: Cincinnati, 55 cases; Henry Ford, 16 cases, Jackson Memorial, 10 cases; and Lakeside, 19 cases.

The procedures recommended for the administration of heparin are described in Appendix D. The method most favored was intermittent intravenous injection which was utilized by 10 hospitals in treating 76 cases, or 66 per cent of those who received heparin Heparin was administered intravenously by continuous drip in 37 cases, or 32 per cent of those who received heparin. Intramuscular injections of heparin in Pitkin's menstruum were given to only 3 cases (Jackson Memorial Hospital). One of these 3 also received heparin by intermittent injection.

FUNCTIONS FOR WHICH HEPARIN WAS USED

The use of heparin in this series was restricted largely to the first three days of anticoagulant therapy, as a supplement to dicumarol. When the prothrombin time had been prolonged sufficiently by the use of dicumarol, heparin was usually discontinued. Only 13 per cent of the total patient-days during the first 3 days of anticoagulant therapy were protected with any heparin even though 87 per cent of all the days of heparin administration fell within this period. Use after the third day was most uncommon. Only 36 days out of a total of 13,597 days of anticoagulant therapy after the third day involved heparin (0.3 per cent of such days).

Because of its use primarily for supplemental purposes, heparin therapy was usually of short duration. It averaged 2.3 days for those receiving any heparin. Its use in this manner is also evident from the fact that heparin was used alone for only 53 patient-days out of a total of 269 days on which any heparin was given. On four-fifths of the days when heparin was administered, patients were also under the influence of dicumarol. Only 3 patients received heparin with no dicumarol supplementation at any time. The detailed counts basic to these figures appear in Appendix F, Table 60.

Relatively speaking, heparin was more frequently the anticoagulant of choice when anticoagulants were resorted to in the control group than in the treated group, it being used for 8 8 per cent of the days of anticoagulant therapy for this group as compared with 1.4 per cent for the treated group. The reason for this discrepancy is clear. Patients in the treated group received dicumarol from the onset, or shortly there-

after, in the vast majority of instances. Patients classified in the control group, however, did not receive anticoagulant therapy unless a thromboembolic episode occurred. At such a time, an immediate anticoagulant effect was imperative. Heparin was administered to such patients promptly and usually in conjunction with dicumarol.

THROMBOEMBOLIC COMPLICATIONS DURING AND FOLLOWING HEPARIN THERAPY

Since heparin was employed in this series primarily to give supplemental protection during the early stages of dicumarol therapy, it is appropriate to ask: Did heparin thus used actually reduce the incidence of thromboembolic complications? The relatively small number of days on which heparin was administered limits the confidence with which this question can be answered. An effort is nevertheless justified since the experience with heparin in most series is even more limited than in the present one.

Complications during the First Three Days

Although experience during the first 3 days of anticoagulant therapy is of special interest, it is difficult to enumerate it statistically on a case basis because of the variety of combinations in which heparin and dicumarol were used. For example, heparin was used sometimes one, sometimes two, and sometimes three or more days and was combined with dicumarol on any or all of these days. Case rates are therefore reported only briefly.

A total of 484 treated group patients received dicumarol only during the first 3 days of anticoagulant therapy. Of these, 8 patients (1.7 per cent of the total) developed a total of 9 thromboembolic complications during these days. Five treated group cases received heparin only during these first 3 days. These 5 cases showed no complications at all during this initial period. Since the number of cases in this group is much too small for rate purposes, it is combined throughout with the group receiving both heparin and dicumarol in this period. The other 88 treated group cases who received anticoagulant therapy received both heparin and dicumarol in any of a number of different combinations during this initial stage. Among these, only 1 case (1.1 per cent) developed a complication. This complication occurred on a day when heparin was not in effect and cannot be termed a failure of heparin. These figures and further case rate details appear in Appendix F Table 61 for those interested.

The general reader can more readily untangle the heparin experience on a day-rate basis, such as is used in the presentation in Table 122 and Figure 126. The treated group in this series received some heparin either alone or in combination with dicumarol on a total of 179 different patient-days during the first 3 days of anticoagulant therapy. During these heparin days not a single thromboembolic complication occurred.[a] In contrast, on those days during the first 3 days of therapy when only dicumarol was being used, a total of 10 thromboembolic complications occurred, a rate of 7.8 per 1000 days of this type for dicumarol.[b]

From these rates it would appear that supplementation with heparin offered perfect protection from thromboembolic complications. Unfortunately, the sample of cases treated with heparin is too small for the difference with respect to complications to be statistically significant.[c] In addition, there is no assurance that the cases treated

[a] The single complication mentioned above as occurring in a case receiving heparin does not appear in the count since it did not occur on a day when heparin was in effect.

[b] For explanation of the day counts used as a base for these rates, see footnote b of Table 122.

[c] Because of technical difficulties, the proportion of cases developing complications on the second day and on the third day were used in these tests rather than the day rates quoted.

with heparin were not a selected group, i.e., a relatively higher risk group than those not selected for heparin supplementation. It would seem probable, rather, that a number of cases selected for extra protection with heparin would be high risk cases, though this hypothesis has not been tested statistically. *It therefore seems logical to infer, in spite of these qualifications, that this favorable rate is due to additional protection afforded by heparin* and is not a chance occurrence although without a much larger sampling of experience with heparin supplementation this cannot be established beyond reasonable doubt.

Of the remaining days of experience with heparin, 63 days consisted of therapy of patients in the control group receiving heparin as an exception,[4] 17 were from the 4th to the 6th day in the treated group, and 10 were after the 6th day in the treated group. These counts in each case afforded too low a basis for rates.

The fact that 1 complication developed when heparin therapy was being used in a control group case (given anticoagulants as an exception) and 1 complication developed later (4th day) under heparin in the treated group serves as a warning that *protection against thromboembolic phenomena is not perfect even with heparin supplementation, in spite of the zero rate shown in Figure 128.*

[4] This experience could not be combined with that for the treated group because it applied to a selected and severely threatened group that would have biased the findings against heparin.

INITIAL HEPARIN AND THROMBOEMBOLIC COMPLICATIONS

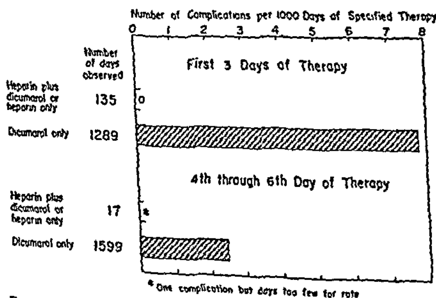


Figure 126. INITIAL HEPARIN AND THROMBOEMBOLIC COMPLICATIONS: Average number of thromboembolic complications developing in the treated group during the first three days and from the fourth through the sixth day of anticoagulant therapy per thousand days when the patient was under dicumarol only and under dicumarol plus heparin, or heparin only. (Rates for the first three days count only half first day as under anticoagulants.)

Complications following the Termination of Heparin

The experience of the present study may be analyzed in addition from a different approach to throw light on a second question of interest: Does heparin merely postpone the onset of complications instead of actually preventing them? To answer this question, the record from the 4th to the 6th day for the 93 cases who received some heparin during the first 3 days and the 484 patients who received only dicumarol in this period was compared (see Appendix F, Table 61). (When heparin was continued beyond the 3rd day, the record for the first 3 days after the termination of heparin was substituted for that for the 4th through the 6th day.) In the group who had previously received dicumarol only, 4 cases (0.9 per cent) developed a complication. In the group who had previously received some heparin, no case developed a complication during the defined period following the termination of heparin. The gain from heparin supplementation in the initial period would appear to be real, not transient.

Observation for this tabulation began on on the 4th day at the earliest and therefore excludes the one case where a pulmonary embolus developed on the 3rd day of anticoagulant therapy after heparin had been discontinued on the second day. In this case the complication developed when the prothrombin time was only 20 seconds (40 per cent). The fact that heparin was discontinued before the prothrombin time had been adequately prolonged affords an obvious explanation of this thromboembolic development. *The results of this analysis therefore give no grounds for a fear that discontinuance of heparin after the initial period will precipitate thromboembolic complications, provided prothrombin times have been adequately prolonged by means of dicumarol prior to discontinuance.*

High Risk Involved in Slow Action of Dicumarol

These analyses had the further incidental result of emphasizing the relatively high risk associated with the first 3 days of therapy with dicumarol. As will be noted in Table 122, the rate of complications developing from the 4th through the 6th day was only 2.5 per 1000 days of therapy as compared with the rate of 7.8 for the first 3 days of therapy. In other words, the rate during the first 3 days with dicumarol only was more than 3 times as high as that for the next 3 days. Coming, as this period does, shortly after the original attack, this period required for dicumarol to prolong the prothrombin time to therapeutic levels is inherently one of high risk, as demonstrated by the rate of 16.4 complications per thousand days at a corresponding stage of the illness in the control group (see Table 95, Chapter VIII). Under these circumstances, protection with a slow-acting anticoagulant such as dicumarol is obviously inadequate.

The record of this study thus affords strong incentive for the use of some type of supplemental protection during these initial days of anticoagulant therapy when chief reliance is placed on dicumarol. Heparin affords the most adequate answer from the point of view of speed but is relatively expensive and requires considerable medical and laboratory time for its administration. The coumarin derivative, 3,3'-carboxymethylenebis (4-hydroxycoumarin) ethyl ester (Tromexan), an anticoagulant put into clinical use in this country after the completion of the clinical aspect of this study, offers another means for somewhat more rapid protection than is possible with dicumarol (see article reproduced in Appendix A). In speed of action it stands midway between heparin and dicumarol. Phenylindanedione apparently acts similarly to Tromexan. While decision as to supplementation and the choice of the agent may

ry from case to case, *the physician plan-ing major reliance on dicumarol for anti-oagulant therapy should always consider he advisability of using another faster-acting nticoagulant such as phenylindanedione luring the period required for dicumarol to take effect.*

HEMORRHAGES UNDER HEPARIN

In order to appraise both the assets and the liabilities of heparin supplementation, the experience with hemorrhages during heparin therapy was also reviewed although the period of possible observation was again very limited. During a total of 209 days on which any heparin was received either alone or in combination with dicumarol, 3 bleeding episodes developed that were considered either due to, or aggravated by, antico-agulants. These episodes consisted of (1) an instance of mild uterine bleeding between menstrual periods believed due either to heparin or to dicumarol in a woman, age 44, with a normal genitourinary history, who was receiving both anticoagulants, (2)

TABLE 122

... UNDER HEPARIN: Number of Thromboembolic Compli- ... the Treated Group on ... d Dicumarol Only, and ... Observed

Type of Anticoagulant Influencing Patient on Given Day	Treated Group (577 Cases)[a]											
	Number of Days Observed					Number of Thromboembolic Complications Diagnosed Clinically					Average Number of Thromboembolic Complications per 1000 Days Observed	
	First Three Days of Anticoagulant Therapy				4th through 6th Day of Anti-coagulants	First Three Days of Anticoagulant Therapy				4th through 6th Day of Anti-coagulants	First 3 Days of Anti-coagu-lants[b]	4th through 6th Day of Anti-coagulants
	Total 1st through 3rd Day[b]	1st Day[b]	2nd Day	3rd Day		Total 1st through 3rd Day[b]	1st Day[b]	2nd Day	3rd Day			
Dicumarol and heparin...	155	76	59	20	8	—	—	—	—	—	0.0	—[c]
Heparin only	24	13	6	5	9	—	—	—	—	1	—[c]	—[c]
Dicumarol only ..	1533	488	509	536	1599	10	—	5	5	4	7.8	2.5
Total, any antico-agulant ..	1712	577	574	561	1616	10	—	5	6	5	7.0	3.1

[a] Excludes cases not receiving anticoagulants because of contraindications Control group cases re-ceiving heparin or dicumarol or both after the development of thromboembolic complications are not included in this tabulation because they are exceptional cases with a high incidence of complications and the number of days observed is small. From the 2nd through the 6th day of therapy, such control cases ... dicu ... plus ... the ... because of complications

[b] Since patients actually were not on anticoagulants during the entire 1st calendar day of therapy (counts reported in column 2 apply to total days), and complications occurring on this 1st day but before the 1st dose of anticoagulants were not counted as occurring during anticoagulant therapy in reports in column 7, the rates reported in column 11 are based on column 7 divided by column 1, minus one-half the number of days reported in column 2 (i.e., each 1st day was arbitrarily considered only a half day in computing this rate).

[c] Rate not reported because of the small number of days of therapy.

an instance of mild hemoptysis believed due to heparin in a patient with no known pulmonary infarction who was receiving both heparin and dicumarol and had a clotting time of one hour and a prothrombin time of 16 seconds, and (3) an instance of severe gross hematuria believed aggravated by heparin in a patient with an indwelling catheter and probably also a renal infarction who was receiving no dicumarol at the time of onset. The first two bleeding episodes cited cleared promptly without the use of heparin antagonists (protamine or toluidine blue) or blood as soon as heparin was discontinued and gave no further difficulty even though dicumarol therapy was continued. In the third instance, heparin was not discontinued and gross hematuria reappeared intermittently for a period of 6 days. It was impossible to tell from the record whether a renal embolus or heparin was responsible, but for statistical purposes it was considered that heparin aggravated the bleeding. This was one of a total of 4 severe bleeding episodes counted as related to anticoagulants in the entire study.

These 3 episodes of bleeding appear insignificant in number, but when they are stated in terms of the period of exposure to risk, the day rate becomes 14.2 bleeding episodes related to heparin (or dicumarol) per thousand days on which any heparin was received (including days when both heparin and dicumarol were in effect).* This rate is noticeably higher than a similar rate for days when only dicumarol was in effect, namely 3.4 episodes per thousand days. Limitation of the rate under dicumarol only to the first week of dicumarol therapy—the period corresponding most closely to the typical period of heparin therapy—does not alter the contrast, for the comparable rate for episodes related to dicumarol for this period was only 3.7 per thousand such days. The number of days of heparin administration is too small, the experience too interwoven with simultaneous use of dicumarol, and the comparability of the cases not sufficiently assured to permit reliable conclusions from the present study as to the comparative hemorrhagic risk with the two anticoagulants. Nevertheless, in the present study the bleeding rates under heparin were sufficiently high to suggest the need for further medical study and evaluation of the hypothesis that the bleeding risk with heparin or heparin plus dicumarol is higher than that with dicumarol only. This experience also suggests that *the physician using heparin supplementation during the initial period of dicumarol therapy as a preventative of thromboembolic phenomena should maintain during this period more than usual watchfulness for hemorrhagic developments.*

* Since patients were considered to have received heparin for only a half day on the first day of anticoagulant therapy, the day count used as a base for this rate was 211 instead of 269 days. Similar corrections have been made in the dicumarol rates quoted here (which therefore do not agree precisely with the rates quoted elsewhere that do not include this relatively minor adjustment for the first day of therapy).

SUMMARY

The experience with heparin in the present study, although too limited to yield statistically significant findings, suggests that probably the use of heparin to supplement dicumarol until prothrombin times have reached the therapeutic range (1) *reduces the risk of thromboembolic complications and* (2) *increases the risk of hemorrhage. Where thromboembolic complications present a significant risk, the assets of heparin are believed greatly to outweigh the increased risk of bleeding.*

CHAPTER XI

Findings on Deaths and Prognosis for Survival in Relation to Anticoagulant Therapy

IN general, deaths are less directly related to anticoagulant therapy than are thromboembolic complications since not all deaths are due to thromboembolic phenomena and not all thromboembolic phenomena produce death. Nevertheless, data on deaths provide a second important measure of the effectiveness of anticoagulants and one that is particularly valuable because it is a net measure that takes into account both the beneficial and the potentially harmful consequences of artificial hypoprothrombinemia.

For this reason, the deaths occurring in this series were analyzed in a variety of ways similar to those applied to thromboembolic complications in Chapter VIII. The analysis deals primarily with three topics: (1) the current prevailing case fatality level in myocardial infarction in the absence of anticoagulant therapy, (2) the characteristics of patients associated with an increased probability of a fatal outcome, and (3) the effectiveness of anticoagulants in reducing deaths.

ACCURACY OF BASIC DATA

Counts for deaths are among the most accurate of any reported in this study. Since a daily record of the period of hospitalization was required for the reports in this series, a failure to report a death would have been immediately obvious. For patients discharged before the end of six weeks, almost complete coverage for the period of the study was achieved by consistent follow-up procedures.* Deaths at home therefore could hardly have been overlooked. Neither does any problem of definition exist. Therefore, the only plausible source of error or underreporting would be incorrect appraisal of the date of onset of the attack. Since only deaths within six weeks of onset were counted, the date of the attack was required and had to be estimated in a few cases. Presumably the errors of such estimates would be compensating and without bias.

The simplicity and accuracy of the death counts were counterbalanced by great difficulty in the assessment of the cause of death and the role of thromboembolic complications in determining the fatal outcome. For example, when a patient already suffering from a large initial infarction and in congestive failure incurred a renal infarction, was the renal infarction the cause of death, or would the patient have died in any case from the original infarction? To emphasize the primary cause of death throughout the analysis would have been uninformative since all patients in the series who died would then have been said to have died of myocardial infarction. On the other hand, if only terminal conditions had been tabulated, thromboembolic complications precipitating

* Only 21 patient-days in the treated group and 30 patient-days in the control group were not covered by follow-up reports. Since deaths within six weeks would normally come to the attention of the physician treating the original myocardial infarction, it is quite improbable that any deaths occurred on these days for which it was impossible to secure a medical report.

terminal uremia or pneumonia would likewise have been overlooked. Because of the difficulties in weighing the role of thromboembolic complications in producing death, the effort was abandoned since this decision seemed preferable to the extensive use of arbitrary decisions to resolve uncertainties.

In consequence, tabulations in the present chapter are confined to a distinction between patients dying in whom one or more thromboembolic complications had been diagnosed clinically at any time during the course of the illness and patients not known at the time of death to have had any thromboembolic complication during the illness. No distinction between complications that did and did not produce death was attempted. Since numerous complications demonstrated at necropsy had not been recognized clinically, the counts in the present chapter for the number of patients dying with prior thromboembolic complications are obviously understated. The chapter on autopsy findings (Chapter XIII) will indicate the approximate size of the correction needed, and the relative degree of understatement for those receiving and not receiving anticoagulants, and will give further details regarding conditions present at the time of death.

GENERAL FINDINGS

Percentage of Cases Dying[b]

The death counts for the present series serve to indicate both the typical prognosis without anticoagulants for cases of this type and the extent to which anticoagulants can affect this prognosis. Even though the counts omit cases dying immediately after the attack, or within the first twenty-four hours of hospitalization, more than one in five of the control group died before the end of six weeks. In actual counts, 96, or 21.7 per cent, of the 442 control group cases died within this relatively short period.[c]

The record of the treated group was considerably better. Of the 589 patients in the treated group, 94, or only 16.0 per cent, died within six weeks of the date of onset.[d] The difference is impressive especially since it occurred in spite of the somewhat indirect relationship of anticoagulants to death. If there were no real difference between the groups, a difference of this amount and in this direction in samples of these sizes would be expected only about once in 100 trials.[e] This difference, moreover, is a net difference, one that takes into account both the losses due to hemorrhage[f] and the savings due to

[b] Throughout this chapter, rates are reported in terms of the percentage of cases in a given sample [illegible] centage). In the usual public health statistics terminology, these would be termed "case fatality [illegible] rate" are used interchangeably, always with the meaning indicated above.

[c] For equivalent rates that would have resulted if other definitions of the control and treated groups had been used, see Appendix F, Table 2.

[d] See footnote c.

[e] The probabilities as stated apply to a difference in one direction only and equal approximately 1.1 in 100, the lower limit of "borderline" as defined for this study (see Appendix C). In a two-direction test, appropriate because of the possibility of a difference in the opposite direction due to losses from hemorrhage, the probability that the difference would occur on a chance basis would be double (i.e., 2.3 per 100). If the death rates are standardized for age and proportion of cases with illness severe at onset, the death rates become 15.4 per cent for the treated group and 22.2 per cent for the control group before corrections for exceptions, a difference of 6.8 per cent. This latter difference is statistically significant with or without regard for the direction of the difference. The approximate 95 per cent confidence limits for the true net difference, between similarly standardized case fatality rates for populations randomly represented by these treatment groups are 2.2 per cent and 11.4 per cent (see footnote b, p. 196).

[f] No deaths due to hemorrhage were identified clinically, but in certain cases, hemorrhage was identified at autopsy as an immediate or contribut-

voidance of thromboembolic episodes. (See page 440 for a discussion of gross and net savings.)

These rates are based on deaths as actually reported before corrections for exceptions in treatment. Actually they understate slightly the chances of death in the control group since 35 of the more severely ill cases in this group received anticoagulants after they had developed one or more complications. As in the case of thromboembolic complications, estimates were undertaken to give a more correct picture of what deaths would be expected if these exceptions had not been made. These estimates were based on the assumption that the actual death rate for cases of similar age and prior complication record in the control group who did not receive any anticoagulants would also have prevailed for these cases if no exceptions had been made. Details of the method are discussed in Appendix B. The estimates are believed to be conservative. They added a total of 7.5 deaths. This addition raised the percentage dying in the control group to 23.4 per cent, presumably a more correct representation of the expected rate without anticoagulants than the uncorrected figure. Similar corrections have been made in death rates throughout this chapter. To simplify the presentation, uncorrected figures are omitted hereafter in the text but can be found in each instance in the corresponding Appendix F tables, together with full related counts. Significance tests, however, have been computed uniformly from the more conservative uncorrected figures. (See explanation of procedures in Appendix C.) These specifications may be assumed to apply throughout the present chapter even though, for purposes of brevity, they are not always reiterated at each point to which they apply.

The basic figures on death rates corrected for exceptions in treatment appear in Table 123 and are shown graphically in Figure 127. Basic death counts appear in Appendix F, Table 63. *In the treated group only 16.0 per cent of the cases died, a rate only about two-thirds of the control group rate of 23.4 per cent.* As would be expected from the indirect and mixed relationship of anticoagulants to death, the contrast is less marked than in the case of complications where the treated group rate of complications per hundred cases was less than one-third of the control group rate. *Nevertheless, it seems clear beyond reasonable doubt that anticoagulants had a substantial and favorable net effect on mortality.*

This overall differential in death rates is largely accounted for by the reduction in cases dying after the development of a thromboembolic complication. This is evident when the percentage of persons dying is subdivided according to the presence or absence of thromboembolic complications during the illness. The percentage of total cases who died and had a known complication prior to death was

ing cause of death (see pp. 438-442) The relationship of such hemorrhages to therapy is difficult to prove or disprove when many conditions occur together in a single case.

TABLE 123

CASES DYING: Percentage of Cases Dying in the Control and Treated Groups and Having or Not Having One or More Clinically Diagnosed Thromboembolic Complications during the Illness

Status of Thromboembolic Complications in Cases Dying	Percentage of Cases Dying[a]	
	Control Group[b] (442 Cases)	Treated Group (589 Cases)
Cases dying and having no clinically diagnosed thromboembolic complication	13.6	12.2
Cases dying and having one or more clinically diagnosed thromboembolic complications	9 8	3.8
All cases dying	23.4	16.0

[a] Basic death counts will be found in Appendix F Table 63.

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

9.8 per cent in the control group after correction for exceptions but only 3.8 per cent in the treated group. This portion of the total percentage dying is shown as the end segment of each bar in Figure 127. This segment of the treated group bar is only about four-tenths the length of the corresponding segment of the control group bar. The reduction is dramatic.

It is perhaps puzzling at first that some slight reduction in the segment relating to deaths without a known complication was also apparent. Slightly fewer of the treated than of the control group (12.2 per cent, treated, *vs.* 13.6 per cent, control) died without a prior complication. While such a difference could easily occur by chance, the autopsy findings (see Chapter XIII) on complications not clinically diagnosed lead one to suspect that it may possibly reflect, in part, the hidden influence of anticoagulants on thromboembolic phenomena of the type usually not diagnosed prior to necropsy.

When the percentages were restated using total deaths as the base, *42 per cent of the control group deaths but only 23 per cent of the treated group deaths were found to have been preceded by a clinically diagnosed complication.* Then chances that such a difference would occur on a chance basis are only about 5 in 100. Since many of the treated group complications actually occurred before effective anticoagulant therapy was instituted, this figure understates the maximum benefits that can be achieved with such therapy.

Death Rates, by Hospital

The death rates thus far reported have referred to the total control and treated

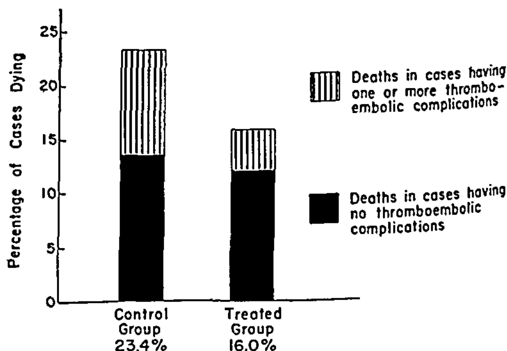


Figure 127. CASES DYING: Percentage of cases dying in the control and treated groups and having or not having one or more thromboembolic complications during the illness.

groups and were arrived at by pooling the experiences of 16 hospitals. Since it was recognized that sufficient cases for a definitive experiment would not be available from any single hospital within a reasonable period of time, the study was originally designed as a cooperative one. Combining the data from a number of hospitals has, indeed, been advantageous, as can be demonstrated by an analysis at this point of the death counts by hospitals (see Appendix F, Table 37). Such an examination will also serve to illustrate the problems that may arise whenever small sample tests of anticoagulants are undertaken or individual physicians attempt to generalize from their own experience.

When the differences between the control and treated groups were considered hospital by hospital, some hospitals showed more marked differences in favor of anticoagulants than did the pooled data, some, lesser, even minimum, differences; and some, actual reversals of the direction of the difference. Examination of these reversals indicates that in all but two instances the hospital samples for either or both the control and treated groups contained less than 25 cases. Moreover, in all but one, the proportion of patients severely ill at onset was considerably higher in the treated than in the control group. These reversals do not, therefore, constitute significant negative evidence.

Further evidence of their lack of significance is provided by the continuation of the study beyond the termination date at Henry Ford Hospital, one of the two hospitals with control and treated group samples above 25 cases that showed a reversal in the present study. In this longer series,[218] which included 731 control and 189 treated cases, this original reversal was not maintained; 26 per cent of the control group cases died as contrasted with only 14 per cent of the treated group cases.

Examination of the statistical significance of the differences between treatment groups for individual hospitals was also undertaken.[a] Only one of these individual hospital differences was statistically significant as defined for this study and only one was of borderline significance. In both of these differences the balance was favorable to anticoagulants. However, in both these hospitals it would be possible to attribute the difference to the fact that considerably more of the control than of the treated patients were severely ill at onset. Consequently, the meaning of the positive evidence was likewise doubtful.

Thus, no single experiment in any given hospital proved definitive with respect to the relation of anticoagulant therapy to survival prospects. Fortunately, however, pooling of the data improved markedly the comparability of the control and treated groups, increased the size of the samples in both treatment groups, and seemed otherwise justifiable.[b] In consequence, the analy-

[a] Hospitals with exceedingly small samples or only one or two deaths [illegible] other [illegible] regard[illegible] none applicable to reversals showed significance.

[b] The pooling of the data in this manner was considered justifiable because: (1) the distribution of cases by hospitals did not differ significantly in the control and treated groups, (2) homogeneity tests applied to the distribution by hospitals of cases dying and cases developing thromboembolic complications (the two major outcomes under study) within the control and treated groups failed on all tests to demonstrate heterogeneity between hospitals that was significant at the one per cent level and gave borderline results on only one of four tests, (3) differences between hospitals in the fatality rate in myocardial infarction have been shown to be largely explainable on the basis of the types of cases admitted,[214] and (4) the types of cases in the control and treated groups were rendered more rather than less comparable by the pooling procedure. The data were pooled without use of artificial weights since (1) data from which weights could be estimated were not available, and (2) the central purpose of the investigation (namely, the testing of anticoagulant therapy) did not require that the total universe of hospitalized myocardial infarction cases throughout the country be accu-

sis of the pooled data gave the definitive results previously reported.

An alternative method of analysis was also tried. Instead of pooling the data, each hospital was treated as an independent small experiment and the probabilities of the differences observed computed. These findings were then combined mathematically by procedures appropriate even when data are nonhomogeneous.[i] These computations led to the same conclusion previously reached with the pooled data, namely, that repeated differences of the amount and direction actually observed in these small experiments would be expected not much more often than once in a hundred samplings if there were no real difference between the treatment groups.[j] *Thus, regardless of the method of analysis, the combination of observations from a number of hospitals makes possible a conclusion not permissible from the individual experiments; namely, that anticoagulants have a favorable effect on the survival prospects of those hospitalized myocardial infarction patients who survive the immediate period after the attack.*

rately characterized, provided the control and treated groups on which anticoagulants were tested were comparable.

[i] The chi square values were transformed into chi values and then summated taking account of the direction of the differences. These were tested for significance against the known standard error of this sum. In this test, some hospitals with exceedingly small samples were grouped into an "all other" category. In applying this procedure it was necessarily assumed that imbalances in individual hospitals in the types of patients in the control and treated groups due to small samples would be compensating and would not lend bias to the total result. Support for this assumption is presented in Chapters IV, V and VI.

[j] The result reported applies to the one-tailed test before correction for exceptions in treatment. The two-tailed test (the one usually quoted) gives probabilities at about the two per cent level. The result should therefore be classified as "borderline" by the strict definitions adopted for this study. As previously indicated, however, either standardization for age and severity or corrections for exceptions in treatment bring the difference into the "significant" class.

Deaths as Reported in Other Studies

The preceding analysis of death counts by hospitals has afforded an excellent illustration of some of the problems involved in drawing conclusions from small samples. Differences in fatality rates found in other studies may have even more diverse sources, among them, the following: (1) the relative severity of the attack in the control and treated group samples, (2) the relative prevalence of other conditions that affect prognosis, (3) whether deaths within the first 24 or 48 hours of hospitalization are included, (4) the adequacy of the prothrombin levels maintained, (5) how long anticoagulant therapy was continued and how early it was begun, (6) how long the patients were observed, (7) the size of the samples observed, (8) any biases resulting from the method of selecting the control and treated groups or from exceptions made in the application or withholding of anticoagulants, and (9) any differences in the type and quality of the medical care received. In view of the multiplicity of possible sources of variation, it is not strange that individual hospitals or individual physicians experimenting with anticoagulants both before and after the present study was undertaken have not always found that their experience repeated that here reported.

Actual evidence from 21 other studies with respect to fatality rates with and without anticoagulants is summarized in Table 124 and Figure 128.[k] Inclusion in the listing was based on the same criteria applied in the compilation of Table 93, Chapter VIII, which shows cases developing thromboembolic phenomena in other studies. These criteria are described on pages 201-202. Other investigators who have reported experiments with anticoagulant therapy in coronary thrombosis with myocardial in-

[k] Kerwin,[104] in a study published subsequent to this tabulation, reports a reduction in mortality rates under anticoagulants which was similar in amount to the reduction achieved in this series.

farction *without control groups* of this type are omitted.

Various possible biases in the data require special comment. For example, in some studies, the record for the treated group was undoubtedly reduced by suboptimal therapy and by the fact that the reporting investigators did not actually supervise the care of some of the patients involved.[274] In a few studies, notably Bresnick et al.,[27] biases were probably introduced in addition by the selective assignment of severe cases to the treated groups, a procedure that would also handicap the treated group. In a number of other studies,[18, 89, 138, 177, 214, 225] control groups were derived from experience prior to the introduction of anticoagulant therapy, when other improvements in therapy had not been developed, a procedure that might increase the control group death rate. Biases in these two directions fortunately counterbalance each other to some extent. In view of the many necessary qualifications, the net result must be considered an approximation only.

In spite of these qualifications, Table 124 is useful in two respects: In the first place, it helps to place the present sample with respect to severity. Control group death rates in the various studies ranged from 13 to 41 per cent and treated group death rates, from 8 to 25 per cent.[1] In both groups, the

[1] Excluding deaths in the first 24 or 48 hours where possible.

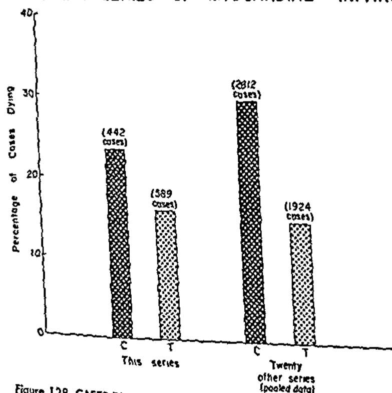


Figure 128. CASES DYING IN THIS SERIES AND TWENTY OTHER SERIES OF MYOCARDIAL INFARCTION: Percentage of cases dying in the control and treated groups in this series and twenty other series (pooled) of myocardial infarction reported in the literature in which anticoagulants were used in the treatment of coronary occlusion with myocardial infarction and for which a control group was provided.

TABLE 124

CASES DYING IN THIS SERIES AND TWENTY-ONE OTHER SERIES OF MYOCARDIAL INFARCTION: Percentage of Cases Dying in the Control and Treated Groups in This Series and in Twenty-One Other Series Reported in the Literature in Which Anticoagulants Were Used in the Treatment of Coronary Occlusion with Myocardial Infarction and for Which a Control Group Was Provided

Author(s)	Number of Cases Observed[a]		Percentage of Cases Dying[b]	
	Control Group	Treated Group	Control Group	Treated Group
1. This series	442	589	23.4[c]	16.0
2. Beckwith & Gage[11]—Chesapeske & Ohio, Clifton Forge, Virginia	100	108	28 0	16 7
3. *Bresnick et al.*[12]—*Boston City*	128	122	12 5	18.9[d]
4. Carmichael & Oetting[40]—U. S. Naval Hospital, Long Beach.	43	30	16.3	13 3
5. Feldman *et al.*[51]—Cook County Chicago:				
Including deaths within 48 hours	76	76	30.3	30 3
Excluding deaths within 48 hours	70	67	24.3	20.9
6. *Furman et al.*[61]—*Vanderbilt University Hospital, Nashville*	261[e]	82[e]	40 2[e]	15.9[e]
7. Greisman & Marcus[76]—Lincoln, New York	100	75	35 0	9 3
8. Hilton *et al.*[81]—Montreal General	38	38	23.7	13 2
9. Holten[91, 92]—Municipal Hospital, Aarhus, Denmark	256	174	35.9	22 4
10. Loudon, Pease & Cooke[131f]—Radcliffe Infirmary, Oxford	125	75	40.8	25 3
11. Manchester & Rabkin[141g]—Gallinger Municipal, Washington, D. C.	150	150	28.0	12.0
12. Mullins *et al.*[146]—Mercy, Pittsburgh	120	174	22.5	7 5
13. Parker & Barker[177]—Mayo, Rochester	100	100	13.0	11 0
14. Peters, Doenges & Brambel[181]—Mercy, Baltimore	86	110	25.6	10 9
15. Rashkoff *et al.*[197]—Mount Sinai, New York	145	142	26.2	12 7
16. Richter, Del Nunzio & Swiller[201]—Coney Island, Brooklyn	150	150	33.3	11.3
17. Schilling[212]—St. Luke's, New York	60	60	40.0	16.7
18. Schnur[216]—Methodist, Jefferson Davis & South Pacific, Houston	...[h]	81	24. [h]	23.5
19. *Smith, Keyes & Denham*[218]—*Henry Ford, Detroit*	731[i]	189[i]	25.6[i]	14 3[i]
20. Tulloch & Gilchrist[226]—Royal Infirmary, Edinburgh.	84	70	40.5	22 9
21. Vander Veer, Marshall & Kuo[236]—Pennsylvania, Philadelphia.	51[i]	35[i]	35.3[i]	8.6[i]
22. Zeluff & Field[246]—Bellevue, New York:				
Including deaths within 48 hours	100	80	40 0	25.0
Excluding deaths within 48 hours	83	70	27.7	14.3
All other series (excluding cases in the present series)	2812	1924	29.5	14.8
All series[j]	3254[k]	2513[k]	28 7[k]	15.0[k]

[a] (: ... the number of different cases observed

... [illegible] ... nd 22 indicate that deaths occurring ... ospital were excluded in both the con- ... ied from study to study from 6 to 72 hours. Where the necessary counts were reported, counts are presented with and without these early deaths.

[c] Data are corrected for exceptions in treatment For method of correction, see Appendix B.

present study rates (23.4, control and 16.0, treated) take a position roughly midway between these extremes. The pooling of 21 of these 22 series[m] yielded an overall percentage dying among control cases of 28.7 per cent and among treated cases, of 15.0 per cent. [Omitting the present series these percentages are 29 5 and 14.8 respectively (see Figure 128).[m]] The present sample is clearly not extreme in severity.[n]

In the second place, Table 124 indicates that the reduction in deaths associated with anticoagulant therapy reported for the present study was also intermediate in amount. The various treated groups included in Table 124 showed death rates that ranged from only about a fourth of the rate for the corresponding control group to a rate somewhat in excess of the control figure. Determination of the reasons for these differences, or lack of differences, would require extended study which is not feasible and would probably also not be successful in some cases.

The general consistency of the direction of the differences is also significant. When deaths within 48 hours are omitted in the figures for Feldman et al.,[44] the 21 studies show only one reversal[o] of the direction and one study with rates that were the same (within one per cent). In all 19 others, the difference favored the treated group. If only chance factors were operating, such a sequence of differences in the same direction would occur less than once in 100 times. Provided the absence of a consistent net bias favoring the treated group can be assumed, this fact in itself constitutes strong evidence in favor of anticoagulants.

If one goes further and takes into account not only the directions, but also the amounts of the various differences, the evidence of a favorable effect on the fatality rate becomes overwhelming. This can be demonstrated by computing the chances that all these various experiments would have yielded independently differences of the observed amounts and directions on a chance basis if there were, in fact, no differences between the control and treated groups. The method is the same as that previously used for the analysis of the individual hospital data with-

[m] One of the series[54] was not included in the pooled rate because control group counts were lacking

[n] Further evidence that the present sample was typical ir ... Doscher ... of 23.5 p ... cases of ... infarction not treated with anticoagulants.

[o] Rates excluding cases dying within 24 or 48 hours are used for these comparisons where available. The one reversal was explained by the investigators Bresnick et al[29] as "partly a reflection of the fact that the anticoagulant was administered out of turn to some of the more severely ill patients."

[d] The authors explain this reversal as "partly a reflecti... ministered out of turn to some of the n...

[e] Subsequent to the above tabulati... by these same authors[37] was received, ... a different number of observations and different mortality rates The trend, however, was the same as in the above figures.

[f] Tromexan was administered to some of the patients in this study.

[g] Some of the patients in this study were treated at home

[h] Rate quoted represents the ... pathological index ra... and the prior case fate... of actual control grou...

[i] Data include cas...

[j] Excludes dea... series 18.

[k] Corrected for ... the present (American Heart) series included in series 19 and 21 Excludes series 18 (see footnote h).

out pooling.[p] The expectation of such a sequence of favorable differences on a chance basis alone in a series of independent experiments is found by such computations to be less than one in a million.[q]

Deaths by Stage of Anticoagulant Therapy

The data available from other studies usually have pertained only to total deaths, to the entire period of observation, and to all types of cases. The data presented thus far for deaths in the present study have been of a similar nature. The remaining sections on deaths, which present data by various subdivisions, will help to clarify the picture further.

The present section deals with the question of when the savings in deaths occurred. Was the lower death rate characteristic only of the period of actual anticoagulant therapy or was the rate lower also when no anticoagulants were being received? Examination of the data from this point of view revealed that 34 of the 94 treated group deaths occurred before anticoagulant therapy could reach an effective level (defined as the fourth day), and 8 others died after the termination of therapy (defined as more than four days after the last dose). Previous comparisons have thus failed to reveal the full contrast in fatality rates during therapy that actually prevailed. To enable one to focus more closely on the period of actual therapy, the rates were refined to make possible a comparison with control group deaths *during comparable periods of the illness.* The method used was similar to the one described on page 206, for complications during corresponding periods of the illness, except that rates are not quoted on a day-rate base since such a base appears inappropriate for a death analysis.

The findings resulting from these computations are given in Table 125. The underlying assumptions of the method are further described in footnote b of this table. Figure 129 presents the findings in graphic form. The short period before therapy and that during the first three days are combined in a single rate since without heparin the chances are minor that treatment can substantially reduce deaths before the fourth day of anticoagulants and since deaths during these days actually may reflect thromboembolic complications prior to therapy. During this early period before effective therapy (which averaged 7 days), 5.8 per cent of the treated group and 6.9 per cent of the control group died—actually an insignificant difference statistically, as would be expected. The period of active anticoagulant therapy; namely, days between the fourth day of anticoagulants and four days after the last dose, inclusive, averaged 26 days in length or was nearly four times as long as the period before active therapy. Death rates for both groups are therefore naturally higher. The marked contrast between the two treatment groups is, however, the striking feature of this period. In the control group, 17.4 per cent of the patients surviving to the beginning of this period died during the period, while of the treated group survivors, 9.5 per cent (or slightly more than half the rate for the control group) died during a corresponding period. The contrast between groups resulting from *focusing* on the period of therapy is thus distinctly greater than the one-third reduction in deaths previously *reported for* the total period.

[p] See footnote i, p. 310 Prior to this test, *corrections* were made for duplication of cases with the present study. Data excluding the first 24 or 48 hours after hospitalization were used where available. Because of the absence of actual control figures for Schnur's study[214] and the closeness of treated and estimated control figures for this study, this study was represented in the test with a zero chi value.

[q] Ratio of sum of chi values to its standard error equals 10.4, a ratio which occurs exceedingly rarely on a chance basis. (In this test, Schnur's study[214] was considered to have a chi value of zero since, as indicated in footnote b of Table 124, actual control group counts were not available.)

This substantial difference during therapy is the more noteworthy since, as was explained in the corresponding section on complications for comparable periods (see Chapter VIII), some selective assignment of severely ill patients to earlier and more prolonged anticoagulant therapy appears to have occurred. Such a selection would increase the probabilities of death in the treated group during the active therapy period and reduce them during the periods before and after therapy. In spite of this handicap to treated group rates during therapy, the difference is statistically significant.

During the seven-day period after termination of therapy the rates returned to levels approximately similar for the two groups, though to much lower levels than before therapy. In contrast to the preceding period under anticoagulants, the difference between treatment groups after termination (1.7, control, *vs.* 2.2, treated) was very minor and far from statistically significant.

In other words, *the difference between the death rate in the control and treated group was significant only during the period when anticoagulant therapy might be expected to be effective. This finding further confirms the conclusion that the difference in deaths was due primarily to the difference in the therapy used and not to any hidden bias in the samples to which this therapy was applied.*

TABLE 125

DEATH RATES BY STAGE OF ANTICOAGULANT THERAPY: Percentage of Cases Dying in the Treated Group during Various Stages of Anticoagulant Therapy and Corresponding Rates for the Control Group for Exactly Comparable Periods of Time

Stage of Anticoagulant Therapy	Treated Group[a]		Percentage of Cases Dying	
	Number of Survivors at Beginning of Period	Number of Deaths	Control Group (Rates artificially computed to cover periods of time exactly comparable to those represented by the various stages of therapy in the treated group)[b]	Treated Group (Rates based on actual data reported)[c]
Before beginning of anticoagulant therapy through 3rd day of therapy[d]	589	34	6.9	5.8
From 4th day of anticoagulant therapy through 4 days after last dose	549	52	17.4	9.5
After termination of anticoagulant therapy	358[e]	8	1.7	2.2

[a] Corresponding counts for the control group are not reported since they were artificially computed and hence have no meaning apart from the rates quoted.

[b] These rates are corrected for exceptions in treatment. They represent what the control group rates would have been if the control group had died at its actual daily rates (corrected for exceptions in treatment) but had been exposed to the risk of death on each day of the illness during each period in numbers that corresponded exactly to the daily number of survivors in the treated group receiving or not re- ceiving anticoagulant therapy during the days in question. Th[illegible] Table 95 (see footnote [illegible] dying. The n[illegible] 40 4, 95 7, anc[illegible] puted, namel[illegible] ceptions in tr[illegible]

[c] If the ag[illegible] unchanged ex[illegible] reduces the ra[illegible]

[d] This peri[illegible] lants because[illegible]

[e] A number [illegible] not observed a[illegible] termination of therapy. [illegible] the 42nd day of their illness and therefore were

Deaths by Week of Illness

Analysis of the death reports according to the number of weeks after the onset of the attack when death occurred adds significant detail both on the changing prognosis for survival in relation to the time after the attack and on the stages of the illness during which anticoagulant therapy showed an observable effect on the death rate. The percentage of survivors from the previous week dying during each week after onset is shown in Table 126, Appendix F Table 62, and Figure 130. In the control group, the maximum risk of death occurred in the second week while deaths in the first week followed closely in second rank.[s] Those who survived these first two critical weeks showed death rates during the third and fourth weeks that were about half the rates that prevailed in the first and second week, while those who survived through the fourth week had excellent prospects since the two final weeks studied both showed death rates of one per cent or less.

Considered in terms of expectation of survival, patients in the control group without anticoagulant protection, had, in retrospect, an 85 per cent chance of surviving through the first two weeks. Those who lived to begin the third week had a 92 per cent chance of surviving through the fourth week, while those who survived to begin the fifth week had a 98 per cent chance of surviving

[s] The fact that the peak occurred in the second week rather than in the first (the more usual pattern) is probably due to (1) the fact that week of illness was carefully computed from the date of onset rather than from the date of hospitalization, (2) the omission of deaths within the first 24 hours, and (3) chance (see footnote t, p. 317).

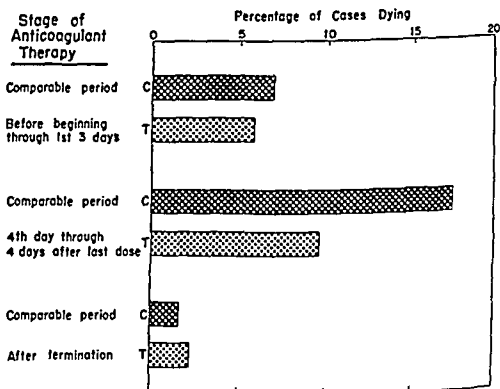


Figure 129. DEATHS BY STAGE OF ANTICOAGULANT THERAPY: Percentage of cases dying in the treated group during various stages of anticoagulant therapy and corresponding rates for the control group for exactly comparable periods of time.

TABLE 126

Week of Illness	Percentage of Cases[a]					
	All Cases Dying		Cases Dying—No Thrombo-embolic Complications		Cases Dying—One or More Thromboembolic Complications	
	Control Group[b]	Treated Group	Control Group[b]	Treated Group	Control Group[b]	Treated Group
First week	7.5	6.8	5.9	5.9	1.6	.9
Second week...	8.4	5.6	4.2	4.7	4.2	.9
Third week	3.8	1.9	1.9	1.1	1.9	.8
Fourth week..	4.4	1.6	1.9	.8	2.5	.8
Fifth week	.7	.6	.6	.2	.1	.4
Sixth week ...	1.0	.4	.3	—	.7	.4

[a] All rates for a given week are based on the same base counts, namely, the total number of survivors at the beginning of each week. These base counts are found in Appendix F Table 62.

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

the six-week period. These percentages would, of course, vary somewhat[s] from these levels if the experiment was repeated. The general pattern is compatible with general clinical experience. *The mortality risk in myocardial infarction is clearly highest in the first two weeks. Therefore, any therapeutic measures which are to have any substantial effect on survival prospects must obviously be applied without delay.*

Approximately the same pattern by weeks was also repeated in the treated group but at a lower level. The treated group differed from the control group pattern only in respect to the earlier beginning of the downward trend and the absence of reversals.[t]

[s] The 95 per cent confidence limits for these percentages cover ranges from 1 to 3 per cent below the figures quoted to 2 to 4 per cent above them.

[t] To test whether these reversals were due to chance, deviations of actual control group death rates by weeks from an assumed smooth curve with no reversals were tested by chi square methods. The hypothesis that they were due to chance could not be disproved even at the 20 per cent level of significance.

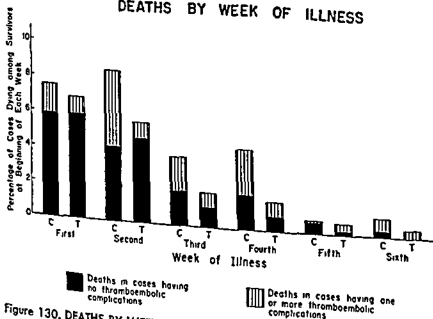


Figure 130. DEATHS BY WEEK OF ILLNESS: Percentage of cases dying and having or not having one or more thromboembolic complications during the illness among survivors in the control and treated groups at the beginning of each week, by week of illness.

Those included in the study had, in retrospect, an 88 per cent chance of surviving through the second week. Those beginning the third week had a 97 per cent chance of surviving through the fourth week, while those beginning the fifth week had a 99 per cent chance of completing the sixth week. The prospects of survival for members of the treated group were greater at each stage of the illness than were those for the control group. From the first through the sixth week in sequence the treated group fatality rates were: 91, 67, 50, 36, 86, and 40 per cent respectively of corresponding control group or "expected" rates. As would be anticipated, the contrasts were in the main the greatest during the second, third, and fourth weeks when the highest proportion of the patients were protected with anticoagulant therapy (see Appendix F, Table 36). *Thus the data by week of illness confirm further the favorable effects of anticoagulant therapy on prognosis for survival.*

Reinspection of Figure 130 reveals further that these differences were largely, though not altogether, due to differences in deaths among patients with one or more thromboembolic complications recognized prior to death. *In no week did the percentage of treated group patients dying and having a recognized thromboembolic complication prior to death exceed one per cent of the total survivors at the beginning of the week, whereas corresponding percentages for the control group showed a maximum above four per cent.* Deaths not preceded by a complication, on the other hand, were approximately identical in rates during the first two weeks, but showed a difference favorable to the treated group thereafter. The fact that this apparently unrelated difference appears specifically during the period of most intensive anticoagulant therapy affords further support for the interpretation given above that it is due to the effects of anticoagulants on the incidence of complications not clinically recognized.

DEATHS IN RELATION TO NONMEDICAL CHARACTERISTICS OF PATIENTS

The remaining analysis of deaths concerned the incidence of deaths among various subgroups of the sample classified according to their general nonmedical characteristics, their medical history, and their medical status at the onset of the illness and during its course. Comment is focused on the variations in prognosis in relation to these characteristics and the extent to which prognosis is improved by anticoagulant therapy. The only nonmedical characteristics that could be used for subgroups in the present study were: age, sex, weight, and economic status as indicated by the type of hospital service received. These nonmedical characteristics are analyzed in relation to deaths in the present section. Subsequent sections will consider the relation of deaths to the patient's medical history and medical status during the illness.

Age

The association of deaths with age is one of the most marked of all relationships demonstrated in the present study. As Table 127, Figure 131, and Appendix F, Table 63 indicate, the actual percentage dying in the control group nearly quadrupled in four decades. In fact, most of the increase occurred in the last two decades (60-79) while the two decade groups below sixty remained on a relative plateau of about 12 per cent or less dying. If the control group findings are restated in terms of survival prospects without anticoagulants, as judged by this study, patients under 50 can be said to have had about seven chances in eight of surviving the six-week period, provided they lived through the first day of hospitalization. In contrast, patients 70 to 79 had only a little better than a fifty-fifty chance of surviving under similar conditions. *It can be concluded that in the absence of anticoagulant therapy, the chances that a patient hospitalized for myocardial in-*

TABLE 127

DEATHS, BY AGE: Percentage of Cases Dying in the Control and Treated Groups and Having or Not Having One or More Thromboembolic Complications during the Illness, by Age

Age Group	Total Cases Observed		Percentage of Cases[a]					
			All Cases Dying		Cases Dying—No Thromboembolic Complications		Cases Dying—One or More Thromboembolic Complications	
	Control Group	Treated Group	Control Group[b]	Treated Group	Control Group[b]	Treated Group	Control Group[b]	Treated Group
Under 40	9	17	—[c]	*5.9*	—[c]	*5.9*	—[c]	—
40-49	72	94	11.5	8.5	8.3	4.2	3.2	4.3
50-59	152	218	12.1	11.0	5.9	8.3	6.2	2.7
60-69	133	172	32 4	19.8	17.3	16.3	15.1	3 5
70-79	70	72	42.1	26 4	27.1	20.8	15.0	5.6
80-89	5	14	—[c]	*57.1*	—[c]	*42.8*	—[c]	*14.3*

Note · *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such rates particularly unstable.*

[a] All rates for a given age and treatment group are based on the same base counts, namely, those cited under "Total Cases Observed"

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[c] Not computed since there were fewer than 10 cases in the sample.

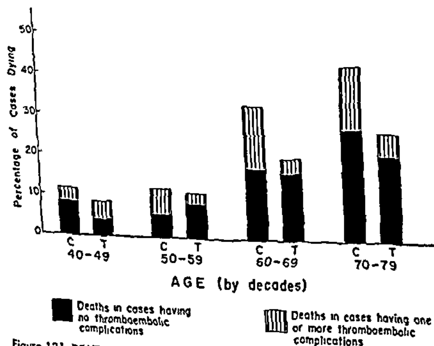


Figure 131. DEATHS, BY AGE: Percentage of cases dying in the control and treated groups and having or not having one or more thromboembolic complications during the illness, by age.

Those included in the study had, in retrospect, an 88 per cent chance of surviving through the second week. Those beginning the third week had a 97 per cent chance of surviving through the fourth week, while those beginning the fifth week had a 99 per cent chance of completing the sixth week. The prospects of survival for members of the treated group were greater at each stage of the illness than were those for the control group. From the first through the sixth week in sequence the treated group fatality rates were: 91, 67, 50, 36, 86, and 40 per cent respectively of corresponding control group or "expected" rates. As would be anticipated, the contrasts were in the main the greatest during the second, third, and fourth weeks when the highest proportion of the patients were protected with anticoagulant therapy (see Appendix F, Table 36). *Thus the data by week of illness confirm further the favorable effects of anticoagulant therapy on prognosis for survival.*

Reinspection of Figure 130 reveals further that these differences were largely, though not altogether, due to differences in deaths among patients with one or more thromboembolic complications recognized prior to death. *In no week did the percentage of treated group patients dying and having a recognized thromboembolic complication prior to death exceed one per cent of the total survivors at the beginning of the week, whereas corresponding percentages for the control group showed a maximum above four per cent.* Deaths not preceded by a complication, on the other hand, were approximately identical in rates during the first two weeks, but showed a difference favorable to the treated group thereafter. The fact that this apparently unrelated difference appears specifically during the period of most intensive anticoagulant therapy affords further support for the interpretation given above that it is due to the effects of anticoagulants on the incidence of complications not clinically recognized.

DEATHS IN RELATION TO NON-MEDICAL CHARACTERISTICS OF PATIENTS

The remaining analysis of deaths concerned the incidence of deaths among various subgroups of the sample classified according to their general nonmedical characteristics, their medical history, and their medical status at the onset of the illness and during its course. Comment is focused on the variations in prognosis in relation to these characteristics and the extent to which prognosis is improved by anticoagulant therapy. The only nonmedical characteristics that could be used for subgroups in the present study were: age, sex, weight, and economic status as indicated by the type of hospital service received. These nonmedical characteristics are analyzed in relation to deaths in the present section. Subsequent sections will consider the relation of deaths to the patient's medical history and medical status during the illness.

Age

The association of deaths with age is one of the most marked of all relationships demonstrated in the present study. As Table 127, Figure 131, and Appendix F, Table 63 indicate, the actual percentage dying in the control group nearly quadrupled in four decades. In fact, most of the increase occurred in the last two decades (60-79) while the two decade groups below sixty remained on a relative plateau of about 12 per cent or less dying. If the control group findings are restated in terms of survival prospects without anticoagulants, as judged by this study, patients under 50 can be said to have had about seven chances in eight of surviving the six-week period, provided they lived through the first day of hospitalization. In contrast, patients 70 to 79 had only a little better than a fifty-fifty chance of surviving under similar conditions. *It can be concluded that in the absence of anticoagulant therapy, the chances that a patient hospitalized for myocardial in-*

period. These large differences are obviously misleading. Standardization for age reduced differences by sex to the relatively slight ones

TABLE 128

DEATHS, BY SEX: Percentage of Cases Dying in the Control and Treated Groups, by Sex

Sex and Treatment Group	Total Cases Observed	Percentage of Cases Dying (Rates Standardized for Age)[a]
Control group:		
Males	346	22.7[b]
Females	96	28.0[b]
Treated group:		
Males	443	16.6
Females	146	17.8

[a] For explanation of process of standardization, see footnote a, Table 101.

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

shown in Figure 132. For samples of the present size they are not statistically significant. *The sex of the patient clearly has, in itself (apart from age), no serious implications for survival prospects once a coronary attack has occurred.* It does, however, influence the prospects of an attack, as has been frequently demonstrated.

Without further refinements and a much larger series it is impossible to tell whether the small differences remaining after standardization are true ones or are due to chance. The fact that for males the percentages dying are lower than for females in both the control and treated groups lends weight to the deduction that some small but real sex difference does exist. If the survival prospects for women with myocardial infarction, age for age, are actually poorer than those for males, as the small differences might

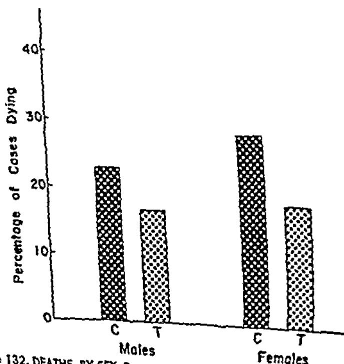


Figure 132. DEATHS, BY SEX: Percentage of cases dying in the control and treated groups, by sex (rates standardized for age).

farction will survive the acute phase of the illness decrease rapidly with age after the sixth decade.

It should be noted that this close association with age does not necessarily demonstrate that age is the cause of this increase. Pathological conditions adversely associated with survival from myocardial infarction tend to be cumulative with age. The observed increase may therefore be due to these associated conditions rather than to age itself, as Russek et al.[208] and Schnur[314] have pointed out. The present findings merely indicate that when a multiplicity of factors cannot be taken into account, age affords a quick approximate index for appraising survival prospects.

The treated group showed a rise in deaths with increasing age similar to that in the control group, but the general level was consistently lower, especially in the older age groups. In sequence by decades beginning at age 40 to 49, percentages were 74, 91, 61, and 63 per cent of corresponding control group rates. *The improvement achieved with anticoagulants seems definitely more conspicuous at the older than at the younger age levels.*[u] Since there was no similarly marked rise with age in the effectiveness of anticoagulants in preventing complications (see Chapter VIII), and since the rise in the incidence of complications by age was of much smaller magnitude, one can surmise that patients at the younger age levels survived thromboembolic complications to which older patients succumbed. This inference is supported by Table 127. It does not follow from this observation, however, that anticoagulant therapy is unimportant at the younger age levels. Thromboembolic complications are potentially grave events regardless of age and may severely handicap a patient either temporarily or permanently.

Particularly conspicuous reductions were obtained at the upper age levels in the percentage of cases dying who had a known complication. For the two older age groups (age 60–69 and 70–79) the treated group percentage was only a third or fourth of that for the control group.[v] Deaths not preceded by a thromboembolic complication were also somewhat lower in the treated than in the control group in the two older age groups and also in the youngest (40–49),[w] a fact which suggests again some influence from anticoagulants other than that which is reflected in clinically diagnosed complications.[x] *Anticoagulants clearly afford the opportunity for substantial saving in life at the older age levels.*

Sex

Sex differences in survival prospects are relatively unimportant in comparison with the marked differences associated with age. The findings in this regard, standardized for age, are given in Table 128, Figure 132, and Appendix F, Table 64. The age adjustment included is particularly important in the case of rates by sex since women do not usually develop coronary thrombosis at as early an age as do men and hence in a myocardial infarction series are usually older (see Chapter IV). In the present series, for example, prior to correction for age differences, the data indicated that 21 per cent of the males and 31 per cent of the females in the control group died, and that similarly, 15 per cent of the males and 20 per cent of the females in the treated group died within the same

[u] Samples by age subgroups are too small to yield statistical significance decade by decade, but [illegible] the difference in [illegible] tional assurance [illegible] with anticoagulants is not a chance one.

[v] The reversal of this relationship which occurred for the age group 40-49 may be due either to chance or some hidden switching of certain severely ill patients in this age group from the control to the treated group to gain for them the benefits of anticoagulant therapy.

[w] The explanation for the reversal in age group 50-59 may be either a failure to recognize thromboembolic complications prior to death or the same phenomenon suggested in footnote v.

[x] Clinically diagnosed thromboembolic complications greatly understate total thromboembolic complications, as Chapter XIII demonstrates

group showed a fatality rate that was less than half that of the control or "expected" rate, a reduction conspicuously greater than that for the other weight groups. *The reduction was, in fact, so great that it almost eliminated in the treated group the excess in mortality characteristic of overweight persons in the control group.* This observation suggests that an excessive tendency to thromboembolism rather than the basic cardiac strain associated with overweight was the major explanation for the high fatality rate of the overweight control group cases. Perhaps a third factor was operating; namely, a lesser ability on the part of obese patients to withstand the added strain of a complication. This interpretation is suggested by the fact that the actual percentage reduction from "expected" complication rates among obese patients in the treated group was less rather than greater than that for the other weight groups (see Chapter VIII). In spite of this finding, a greater saving in life was accomplished. *In view of the exceptional benefits that overweight persons apparently can derive from anticoagulant therapy, it is particularly important that obese persons with myocardial infarction receive early and fully adequate anticoagulant protection.*

Type of Hospital Care

The only other general category available for the classification of patients was that for type of hospital service received. Under present conditions such data can serve as a

DEATHS BY WEIGHT STATUS

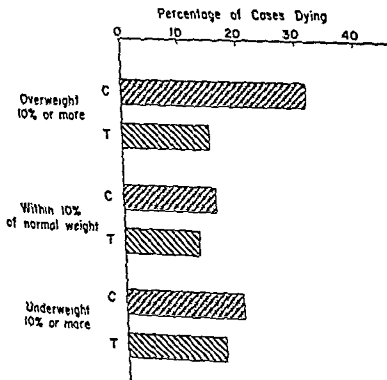


Figure 133. DEATHS BY WEIGHT STATUS: Percentage of cases dying in the control and treated groups, by weight status in relation to normal (rates standardized for age).

suggest, perhaps the explanation lies in the higher prevalence of diabetes and hypertension in women (see Chapter IV) and the higher than average death rates found associated with these conditions in the present study (see pages 326–328).

Weight

Analysis of the data on deaths by weight in relation to normal yielded more striking contrasts than did that by sex. The findings, again standardized by age and corrected for exceptions in treatment, are given in Table 129 and Figure 133. Supporting data appear in Appendix F, Table 65. As previously, underweight and overweight were defined as deviations of 10 per cent or more from the average weight for persons of the same sex, height, and age. About the same proportion of the control and treated groups were 10 per cent or more overweight (control group, 23 per cent; treated group, 22 per cent, excluding unknowns). Unfortunately, however, 149 patients could not be classified by weight status due to the absence of necessary information (usually height). The excessively small numbers in some age subgroups that resulted make appropriate an extra measure of caution in the use of the figures.

TABLE 129

DEATHS IN RELATION TO WEIGHT STATUS: Percentage of Cases Dying in the Control and Treated Groups, by Weight Status in Relation to Normal

Weight Status in Relation to Normal and Treatment Group	Total Cases Observed[a]	Percentage of Cases Dying (Rates Standardized for Age)[b]
Control group:		
10% or more overweight	68	32.0[c]
Within 10% of normal weight	164	16 2[c]
10% or more underweight	61	20.6[c]
Treated group:		
10% or more overweight	90	15 2
Within 10% of normal weight .	239	13 1
10% or more underweight .	84	17.1

[a] Because of lack of a report of height or weight or age, the weight status of 149 control group cases and 176 treated group cases could not be computed. Death rates for these cases of unknown weight appear in Appendix F Table 65

[b] For explanation of process of standardization, see footnote a, Table 101.

[c] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

In spite of these limitations, the findings were striking in two respects: (1) the very high mortality among overweight persons in the control group and (2) the marked reduction in the percentage dying among overweight patients treated with anticoagulant therapy. *The mortality among the overweight control group patients was almost exactly double that for persons of normal weight* (32 per cent *vs.* 16 per cent). This finding is consistent with the common observation that overweight is adversely associated with longevity.[8] Even though the samples were small, a difference of such a marked amount and in this direction would be expected on a chance basis alone less than once in 100 times. Since very high thromboembolic complication rates also characterized the overweight group (see Chapter VIII), it may be assumed that their high mortality was due, at least in part, to their excessive incidence of complications. The strain on a damaged myocardium of maintaining in circulation the large blood volume needed by overweight persons, was, no doubt, a second factor. In contrast to overweight persons, persons of normal weight had the most favorable mortality record of any control group weight class. Underweight persons took an intermediate position. Since there is little reason to believe that underweight in itself would reduce survival prospects, it is to be presumed that both their underweight and their somewhat unfavorable survival record were due to a common factor, at least in some instances.

It is further noteworthy that the *reduction in mortality associated with anticoagulant therapy was greatest in the overweight group.* Patients in this component of the treated

among those receiving private or semiprivate service.

This difference suggests a related question: Could the favorable general survival record of the treated group already reported as seemingly due to anticoagulant therapy be due rather to the somewhat excessive proportion of ward cases in the control group (see Chapter VII)? This question can be answered by combining the death rates reported in this section, already standardized for age, in such a way that the proportion of ward and private cases is the same in both the control and treated groups as in the total sample. When this is done, the percentage dying in the control group becomes 22.5 instead of 23.4 per cent and in the treated group, 16.4 instead of 16.0 per cent. This further correction obviously has only minor consequences. *A very substantial difference in fatality rates by treatment groups remains that cannot be explained in terms of the proportion of ward cases in the control group.*

The conclusion that anticoagulant therapy was the major factor responsible for the difference in death rates is further substantiated by *the fact that a favorable association between anticoagulant therapy and improved survival prospects was found for both private and semiprivate cases and ward cases.* The treated group private and semiprivate fatality rate was 58 per cent of that for the control group. The treated group ward fatality rate was 77 per cent of that for the control group. This somewhat lesser improvement in death rates associated with anticoagulant therapy found for ward cases probably reflects the same differences in type of patient and type of care previously men-

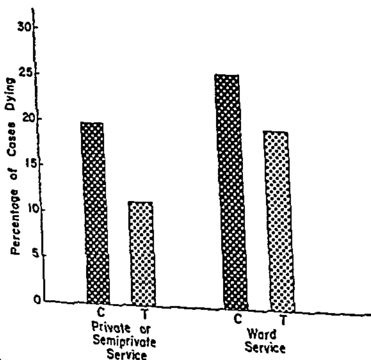


Figure 134. DEATHS BY TYPE OF SERVICE: Percentage of cases dying in the control and treated groups among patients receiving private or semiprivate care and among patients receiving ward care (rates standardized for age).

rough index of economic status. The findings appear in Table 130, standardized for age and corrected for exceptions in treatment. They may be grasped rapidly from Figure 134 where they are presented graphically. Detailed counts appear in Appendix F, Table 66.

A fatality rate substantially higher than for private patients appears to be characteristic of ward patients with myocardial infarction. In the control group, the percentage of private and semiprivate cases dying was about one-fifth less than that for ward cases and in the treated group, more than two-fifths less than the ward rate. The difference in the treated group is sufficient to be of borderline statistical significance as defined for this study. Since, in addition, it is repeated in the control group, it is probably not due to chance.

The data do not reveal the reason for this difference. It cannot be attributed to complications since practically no difference by type of service was found in the incidence of thromboembolic phenomena (see Chapter VIII). For this same reason it cannot be due to a difference (if any) in the care with which anticoagulant therapy was supervised on the wards and private services, for one would expect that any such difference would be reflected in the complication rate. Perhaps the more intensive and individualized medical and nursing care characteristic of private and semiprivate service tended in general to increase the patient's prospects for survival from myocardial infarction. Since, in addition to differences in basic service, 22 per cent of the private and semiprivate patients in the present series received the services of a private duty nurse as compared with 3 per cent of the ward cases, some difference in survival record might be expected. Perhaps ward cases also tended to be in poorer condition physically than private patients at the time of admission. Although there is relatively little direct evidence to support this interpretation,[f] examination of deaths by hospitals revealed that the death rates in the large public hospitals that contributed heavily to the ward group in the present series were in general higher than those for the hospitals contributing mainly private patients. Differences in the type of patient served must play some role in this result, for it seems reasonable to expect relatively high death rates under stress among patients from the lower income groups who are often unable to protect their health from the strain of unsuitable occupations and other adverse conditions. Whatever the reason, the prospects of survival from myocardial infarction, as judged from this series, *appear to be somewhat lower among ward cases than*

TABLE 130

DEATHS, BY TYPE OF SERVICE: Percentage of Cases Dying in the Control and Treated Groups among Patients Receiving Private or Semiprivate Care and among Patients Receiving Ward Care

Type of Service and Treatment Group	Total Cases Observed[a]	Percentage of Cases Dying (Rates Standardized for Age)[b]
Control group:		
Private or semiprivate	155	19.8[c]
Ward	281	25.2[c]
Treated group:		
Private or semiprivate	221	11.4
Ward	343	19.4

[a] Tabulation omits 6 cases in the control group and 25 cases in the treated group who received both ward and private or semiprivate care at different times during the period of observation

[b] For explanation of process of standardization, see footnote a, Table 101.

[c] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[f] The percentage of cases severely ill at onset was the same (within 1 percentile point) for both private and semiprivate and ward cases. Twenty-four per cent of the ward cases as compared with 22 per cent of the private and semiprivate cases were known to have had a previous infarction. Since there was evidence of underreporting of previous infarctions for the ward group (see pp. 328-329), the actual difference was probably greater than these percentages reveal. Other characteristics were not tabulated by type of service.

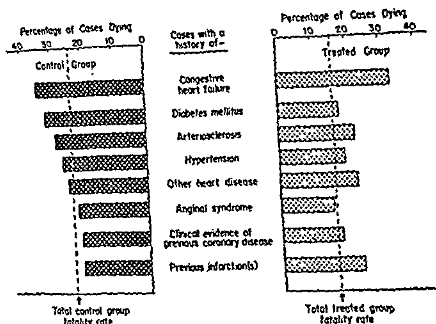


Figure 135. DEATHS IN RELATION TO A POSITIVE MEDICAL HISTORY OF VARIOUS CONDITIONS: Percentage of cases dying in the control and treated groups among patients with a positive history of various conditions.

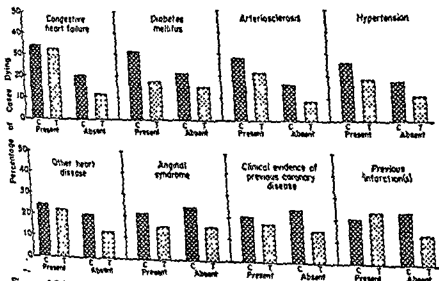


Figure 136. DEATHS IN RELATION TO A POSITIVE OR NEGATIVE MEDICAL HISTORY OF VARIOUS CONDITIONS: Percentage of cases dying in the control and treated groups among patients with a positive or negative history of various conditions (rates for clinical evidence of previous coronary disease and previous infarction standardized for age).

tioned as possible explanations for the general difference in death rates by type of service.

DEATHS IN RELATION TO MEDICAL HISTORY

In addition to tabulation of deaths in relation to the characteristics of patients at the time of the attack, the fatality records with and without anticoagulants were analyzed in relation to the patient's medical history. The types of conditions in the medical history which could be considered in this analysis were greatly limited by the small numbers of patients with a positive history of some of the conditions of interest, since sound fatality rates could not be based on such small numbers. Relationships that could *not* be explored for this reason included variations in mortality with auricular fibrillation, thrombophlebitis, hepatic and renal disease, gallbladder disease, gout, gangrene, and various types of operations. Only conditions found positive in the history of at least 40 patients in each treatment group are considered in Table 131. A total of eight conditions met this qualification. The rates quoted have not been standardized for age except in the case of "clinical evidence of previous coronary disease" and "previous infarctions." In these instances, the correction resulted only in very minor changes in rates. Further details are given in Appendix F, Table 67. Figure 135 presents the control group rates in descending order for those with a positive history of each condition and permits comparisons with the treated group and with general death rates for both groups. In Figure 136, the same data are again presented, this time rearranged to permit an easier comparison of the control and treated groups. Rates for those with a negative history of given conditions have also been added.

Of the eight conditions charted, congestive

TABLE 131

DEATHS IN RELATION TO A POSITIVE OR NEGATIVE MEDICAL HISTORY OF VARIOUS CONDITIONS: Percentage of Cases Dying in the Control and Treated Groups among Patients with a Positive or Negative Medical History of Various Conditions

Condition in Medical History	Total Cases Observed[a]				Percentage of Cases Dying[b]			
	Present		Absent		Present		Absent	
	Control Group	Treated Group	Control Group	Treated Group	Control Group[c]	Treated Group	Control Group[c]	Treated Group
Coronary artery disease:								
Anginal syndrome	223	285	205	285	21.7	15.4	24.7	15 8
[illegible]	99	123	313	427	20.6[d]	23.5[d]	23.4[d]	13.5[d]
[illegible] nary disease	269	334	139	209	20.9[d]	17.6[d]	24 5[d]	14.8[d]
Other cardiac history:								
Congestive heart failure	66	82	364	489	34.2	32 9	20.7	11.9
Other heart disease	44	67	360	462	24.5	22.4	20.7	12 3
Cardiovascular and other conditions:								
Arteriosclerosis	209	246	192	300	28 4	22.0	16.3	9 0
Hypertension	148	221	229	295	26.2	19.0	17.9	11.5
Diabetes	51	62	384	517	31.8	17.7	21.6	15 3

[a] In a number of instances adequate histories could not be obtained. Such cases were not included under either "present" or "absent." To secure number of these unknowns for each category, subtract the totals of "present" and "absent" from 442 for the control group and 589 for the treated group

[b] Based on number of cases with and without condition in history.

[c] Data are corrected for exceptions in treatment. For method of correction, see Appendix B and footnote b, Appendix F, Table 67

[d] Rates are standardized for age.

cardiograms taken during hospitalization.[16] Such underreporting could easily have produced a spurious increase in the death rate of those with a negative history and a spurious decrease in the death rate of those with one or more previous infarctions. The fact that the same reversal did not occur in the treated group suggests further that chance factors and occasional hidden shifts to the treated group of seriously ill patients with a history of a previous myocardial infarction (see page 9) may also have contributed to the unexpected result. Because of these possibilities and the confirmation of the usual *pattern* in most subgroups, *the contradictory control group findings* cannot be considered a challenge to the usual belief that patients who have had a previous infarction have a poorer chance of surviving subsequent infarctions than those without such a record.

The group labelled "clinical evidence of previous coronary disease" is a *composite* of cases for whom any one or more of the following [illegible] previou[illegible] syndron[illegible] reflects in the control group the same favorable death rates for those with a positive history of previous coronary disease as did two of the component categories (see Table 131 and Figure 136). The explanations postulated for the anginal syndrome findings and the previous infarction findings thus are again pertinent. The relatively low death rates for those with a *positive* history suggest that coronary artery disease does not affect the immediate prognosis unfavorably once a myocardial infarction has developed.

[16] Thirty-seven per cent of ward cases but only 27 per cent of private and semiprivate cases reported to have had previous infarctions showed residual evidence of an old infarction on EKG's taken during the illness. If it is assumed that the percentage with residual EKG evidence should have been the same in the two groups and that overreporting in the history did not occur, it can be demonstrated that underreporting of a history of previous infarctions occurred in 53 ward cases.

Other conditions not tabulated for which actual deaths were high in proportion to the number with a positive history were renal disease, thrombophlebitis, cerebral accidents, and auricular fibrillation. Base counts for these conditions, however, were too low for tabulation or graphic presentation of death rates. The record for gallbladder disease and hepatic disease, on the other hand, was not consistent as between the two treatment groups.

Re-examination of Figure 136 from the point of view of the relative effects of anticoagulants in different conditions leads to the further observation that, with a single exception, a differential, sometimes small, sometimes large, in favor of anticoagulant therapy was found for all the conditions tabulated. In view of the strong possibility of errors in classification previously mentioned, the single reversal of the usual pattern that occurred in the "previous infarctions" category cannot be considered as evidence that anticoagulants are contraindicated among such cases. Because of the lack of comparability in age, the details of the history, and the severity of the previous pathology and because of the small size of some of the groups, the differing ratios of improvement with anticoagulant therapy cannot be considered significant. It is nevertheless interesting that in all conditions characterized by arteriosclerosis or coronary artery disease the reduction in deaths associated with anticoagulant therapy was greater among those with a negative than among those with a positive history of the condition.

DEATHS IN RELATION TO CONDITIONS PRESENT EARLY IN THE ILLNESS

In addition to the general characteristics of patients and their medical history, the physician has available to him for purposes of prognosis the condition of the patient during the early *period* of his illness im-

failure and diabetes showed the poorest survival records. While the lack of a correction for age in these rates may be a factor in this lead, the evidence of a poor prognosis is in accord with clinical experience. These conditions were followed in descending order by arteriosclerosis, hypertension, and other forms of heart disease. All showed fatality rates above the general average for the control group and above those for cases with a negative history for the same condition. Some of these differences were statistically significant.* In the treated group these same conditions likewise showed above average death rates, but their rank order was somewhat different. Congestive failure again topped the list. The meaning, if any, of the change in the rank order of diabetes is not clear. Chance variations in the severity of this or other conditions in these patients may be responsible.

For the remaining conditions tabulated, the findings appear in some respects to run counter to expectation. Patients with a previous record of anginal syndrome showed, for example, a slightly better than average death rate in both the control and treated groups. This observation was further confirmed by comparisons with the death rates for those with no history of anginal syndrome. These comparisons failed to reveal any significant difference between those with, and those without, a history of angina. Since anginal pain is dramatic and is subjectively experienced, it seems unlikely that the absence of difference could be due to underreporting of the syndrome. The findings therefore suggest that among coronary thrombosis cases of the type studied, those who have previously experienced anginal attacks have at least as good a chance of surviving the attack as do those who have not shown this syndrome. This finding is consistent with the observations of Mintz and Katz.[181] Perhaps most cases subject to the anginal syndrome have had coronary artery disease for a sufficient period to have developed compensating collateral circulation which, in turn, stands them in good stead when a myocardial infarction occurs. Perhaps such cases are also more aware of their condition and seek and receive more adequate and prompt medical help in the emergency of the attack.

The interpretation of the findings for cases with and without one or more previous infarctions is open to more doubt. Again the expectation of higher death rates for those with a positive history than for those without such a record was not fully confirmed. In this case, however, the control and treated groups presented contradictory evidence. The anticipated relationship appeared only in the treated group. Moreover, further breakdown of the findings indicated that only the ward cases in the control group failed to show the anticipated higher death rate for cases with a previous infarction than for those without such a history. While the difference, though substantial,** does not exceed that which can reasonably be attributed to chance, one is nevertheless led to suspect that underdiagnosis and underreporting of previous infarctions among the economically less fortunate led to including in the "no previous infarction" group some patients who actually had had a prior infarction. This view is supported by the difference between ward and private cases in the proportion of reported previous infarctions actually showing up on electro-

* Selected comparisons of the percentage of cases dying among those with and without given conditions within the same treatment group showed highly significant differences in the case of congestive failure (treated group) and arteriosclerosis (treated group), significant differences in the case of arteriosclerosis (control group), and "borderline" differences in the case of congestive failure (control group) and hypertension (treated group). Other differences were either not sufficient to be significant with the size of the samples involved or were not tested.

** Among control group ward cases, 50 (25 6 per cent) of 195 cases with no previous infarction died and 9 (13 4 per cent) of 67 cases with one or more previous infarctions died.

[c]ardiograms taken during hospitalization.[56] [S]uch underreporting could easily have [p]roduced a spurious increase in the death [r]ate of those with a negative history and a [s]purious decrease in the death rate of those with one or more previous infarctions. The fact that the same reversal did not occur in the treated group suggests further that chance factors and occasional hidden shifts to the treated group of seriously ill patients with a history of a previous myocardial infarction (see page 9) may also have contributed to the unexpected result. Because of these possibilities and the confirmation of the usual pattern in most subgroups, the contradictory control group findings cannot be considered a challenge to the usual belief that patients who have had a previous infarction have a poorer chance of surviving subsequent infarctions than those without such a record.

The group labelled "clinical evidence of previous coronary disease" is a composite of cases for whom any one or more of the following was reported: a previous infarction, previous coronary artery disease, or anginal syndrome. Consequently it reflects in the control group the same favorable death rates for those with a positive history of previous coronary disease as did two of the component categories (see Table 131 and Figure 136). The explanations postulated for the anginal syndrome findings and the previous *infarction* findings thus are again pertinent. The relatively low death rates for those with a positive history suggest that coronary artery disease *does not* affect the immediate prognosis unfavorably once a myocardial infarction has developed.

[56] Thirty-seven per cent of ward cases but only 27 per cent of private and semiprivate cases reported to have had previous infarctions showed residual evidence of an old infarction on EKG's taken during the illness. If it is assumed that the percentage with residual EKG evidence should have been the same in the two groups and that overr... be de... of pr...

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DEATHS IN RELATION TO CONDITIONS PRESENT EARLY IN THE ILLNESS

In addition to the general characteristics of patients and their medical history, the physician has available to him for purposes of prognosis the condition of the patient during the early period of his illness im-

failure and diabetes showed the poorest survival records. While the lack of a correction for age in these rates may be a factor in this lead, the evidence of a poor prognosis is in accord with clinical experience. These conditions were followed in descending order by arteriosclerosis, hypertension, and other forms of heart disease. All showed fatality rates above the general average for the control group and above those for cases with a negative history for the same condition. Some of these differences were statistically significant.[*] In the treated group these same conditions likewise showed above average death rates, but their rank order was somewhat different. Congestive failure again topped the list. The meaning, if any, of the change in the rank order of diabetes is not clear. Chance variations in the severity of this or other conditions in these patients may be responsible.

For the remaining conditions tabulated, the findings appear in some respects to run counter to expectation. Patients with a previous record of anginal syndrome showed, for example, a slightly better than average death rate in both the control and treated groups. This observation was further confirmed by comparisons with the death rates for those with no history of anginal syndrome. These comparisons failed to reveal any significant difference between those with, and those without, a history of angina. Since anginal pain is dramatic and is subjectively experienced, it seems unlikely that the absence of difference could be due to underreporting of the syndrome. The findings therefore suggest that among coronary thrombosis cases of the type studied, those who have previously experienced anginal attacks have at least as good a chance of surviving the attack as do those who have not shown this syndrome. This finding is consistent with the observations of Mintz and Katz.[152] Perhaps most cases subject to the anginal syndrome have had coronary artery disease for a sufficient period to have developed compensating collateral circulation which, in turn, stands them in good stead when a myocardial infarction occurs. Perhaps such cases are also more aware of their condition and seek and receive more adequate and prompt medical help in the emergency of the attack.

The interpretation of the findings for cases with and without one or more previous infarctions is open to more doubt. Again the expectation of higher death rates for those with a positive history than for those without such a record was not fully confirmed. In this case, however, the control and treated groups presented contradictory evidence. The anticipated relationship appeared only in the treated group. Moreover, further breakdown of the findings indicated that only the ward cases in the control group failed to show the anticipated higher death rate for cases with a previous infarction than for those without such a history. While the difference, though substantial,[**] does not exceed that which can reasonably be attributed to chance, one is nevertheless led to suspect that underdiagnosis and underreporting of previous infarctions among the economically less fortunate led to including in the "no previous infarction" group some patients who actually had had a prior infarction. This view is supported by the difference between ward and private cases in the proportion of reported previous infarctions actually showing up on electro-

[*] Selected comparisons of the percentage of cases dying among those with and without given conditions within the same treatment group showed highly significant differences in the case of congestive failure (treated group) and arteriosclerosis (treated group), significant differences in the case of arteriosclerosis (control group), and "borderline" differences in the case of congestive failure (control group) and hypertension (treated group). Other differences were either not sufficient to be significant with the size of the samples involved or were not tested.

[**] Among control group ward cases, 50 (25 6 per cent) of 195 cases with no previous infarction died and 9 (13 4 per cent) of 67 cases with one or more previous infarctions died.

diograms taken during hospitalization.[bb] h *underreporting* could easily have duced a spurious increase in the death e of those with a negative history and a rious decrease in the death rate of those th one or more previous infarctions. The t that the same reversal did not occur in e treated group suggests further that ance factors and occasional hidden shifts the treated group of seriously ill patients ith a history of a previous myocardial farction (see page 9) may also have conibuted to the unexpected result. Because f these possibilities and the confirmation f the usual pattern in most subgroups, he contradictory control group findings annot be considered a challenge to the usual belief that patients who have had a previous infarction have a poorer chance of surviving subsequent infarctions than those without such a record.

The group labelled "clinical evidence of previous coronary disease" is a composite of cases for whom any one or more of the following was reported: a previous infarction, previous coronary artery disease, or anginal syndrome. Consequently it reflects in the control group the same favorable death rates for those with a positive history of previous coronary disease as did two of the component categories (see Table 131 and Figure 136). The explanations postulated for the anginal syndrome findings and the previous infarction findings thus are again pertinent. The relatively low death rates for those with a positive history suggest that coronary artery disease does not affect the immediate prognosis unfavorably once a myocardial infarction has developed.

[bb] Thirty-seven per cent of ward cases but only 7 per cent of private and semiprivate cases reported to have had previous infarctions showed residual evidence of an old infarction on EKG's taken during the illness. If it is assumed that the percentage with residual EKG evidence should have been the same in the two groups and that overreporting in the history did not occur, it can be demonstrated that underreporting of a history of previous infarctions occurred in 53 ward cases.

Other conditions not tabulated for which actual deaths were high in proportion to the number with a positive history were renal disease, thrombophlebitis, cerebral accidents, and auricular fibrillation. Base counts for these conditions, however, were too low for tabulation or graphic presentation of death rates. The record for gallbladder disease and hepatic disease, on the other hand, was not consistent as between the two treatment groups.

Re-examination of Figure 136 from the point of view of the relative effects of anticoagulants in different conditions leads to the further observation that, with a single exception, a differential, sometimes small, sometimes large, in favor of anticoagulant therapy was found for all the conditions tabulated. In view of the strong possibility of errors in classification previously mentioned, the single reversal of the usual pattern that occurred in the "previous infarctions" category cannot be considered as evidence that anticoagulants are contraindicated among such cases. Because of the lack of comparability in age, the details of the history, and the severity of the previous pathology and because of the small size of some of the groups, the differing ratios of improvement with anticoagulant therapy cannot be considered significant. It is nevertheless interesting that in all conditions characterized by arteriosclerosis or coronary artery disease the reduction in deaths associated with anticoagulant therapy was greater among those with a negative than among those with a positive history of the condition.

DEATHS IN RELATION TO CONDITIONS PRESENT EARLY IN THE ILLNESS

In addition to the general characteristics of patients and their medical history, the physician has available to him for purposes of prognosis the condition of the patient during the early period of his illness im-

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** Among control group ward cases, 50 (25.6 per cent) of 195 cases with no previous infarction died and 9 (13.4 per cent) of 67 cases with one or more previous infarctions died.

cardiograms taken during hospitalization.[56] Such underreporting could easily have produced a spurious increase in the death rate of those with a negative history and a spurious decrease in the death rate of those with one or more previous infarctions. The fact that the same reversal did not occur in the treated group suggests further that chance factors and occasional hidden shifts to the treated group of seriously ill patients with a history of a previous myocardial infarction (see page 9) may also have contributed to the unexpected result. Because of these possibilities and the confirmation of the usual pattern in most subgroups, the contradictory control group findings cannot be considered a challenge to the usual belief that patients who have had a previous infarction have a poorer chance of surviving subsequent infarctions than those without such a record.

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Re-examination of Figure 136 from the point of view of the relative effects of anticoagulants in different conditions leads to the further observation that, with a single exception, a differential, sometimes small, sometimes large, in favor of anticoagulant therapy was found for all the conditions tabulated. In view of the strong possibility of errors in classification previously mentioned, the single reversal of the usual pattern that occurred in the "previous infarctions" category cannot be considered as evidence that anticoagulants are contraindicated among such cases. Because of the lack of comparability in age, the details of the history, and the severity of the previous pathology and because of the small size of some of the groups, the differing ratios of improvement with anticoagulant therapy cannot be considered significant. It is nevertheless interesting that in all conditions characterized by arteriosclerosis or coronary artery disease the reduction in deaths associated with anticoagulant therapy was greater among those with a negative than among those with a positive history of the condition.

DEATHS IN RELATION TO CONDITIONS PRESENT EARLY IN THE ILLNESS

In addition to the general characteristics of patients and their medical history, the physician has available to him for purposes of prognosis the condition of the patient during the early period of his illness im-

TABLE 132

DEATHS, BY SEVERITY OF ILLNESS AT ONSET: Percentage of Cases Dying in the Control and Treated Groups, by Severity of Illness at Onset

Severity at Onset and Treatment Group	Total Cases Observed	Percentage of Cases Dying (Rates Standardized for Age)[a]
Control group:		
Cases severe at onset......	116	48.8[b]
Cases mild or moderate at onset....................	326	14.0[b]
Treated group:		
Cases severe at onset......	181	35.2
Cases mild or moderate at onset.....................	408	7.2

[a] For explanation of process of standardization, see footnote a, Table 101.

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

mediately following the attack. To shed light on the choice to be made from among available first-week criteria for predicting survival prospects, analyses of deaths are presented in this section by the following subgroups: severity at onset, good and poor risk criteria, development of thromboembolic complications, location of infarction, abnormal rhythms, and congestive heart failure and shock.

Severity at Onset

The first and most obvious criterion available for the prediction of survival prospects is the physician's evaluation of severity at onset. The findings in this regard are given in Table 132, Appendix F Table 68, and Figure 137. *These in combination present unmistakable evidence that the phy-*

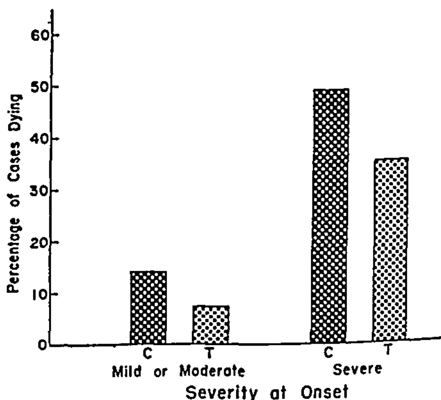


Figure 137. DEATHS BY SEVERITY OF ILLNESS AT ONSET: Percentage of cases dying in the control and treated groups, by severity of illness at onset (rates standardized for age).

sician's appraisal of severity at onset has high predictive value. Of patients in the control group judged severely ill at onset, almost half died before the end of six weeks, whereas only about 1 in 7 died among those considered only mildly or moderately ill at onset. Similarly, in the treated group slightly more than a third of those severely ill at onset died as contrasted with about 1 in 14 among those mildly or moderately ill. These rates have been standardized for age and the resulting differences are highly significant statistically. Therefore they cannot reasonably be explained by chance or by age differences in subgroups. *The data thus demonstrate that the outlook for survival among myocardial infarction patients judged severely ill at onset is indeed grave and validate the soundness of the physician's judgment as to severity at onset.*

Fortunately this poor prognosis can be mitigated somewhat by anticoagulant therapy. The fatality rate among patients severely ill at onset in the treated group was only about seven-tenths of the control group rate. Even in respect to such savings, however, the severely ill were at a disadvantage since those with only mild or moderate symptoms showed a treated group rate only five-tenths of the corresponding control group rate.[**]

An incidental observation suggested by Appendix F Table 68 is that the categorizing of pati[illegible]

[illegible] of patients dying within each severity subgroup climbed as the older age levels were reached It would thus appear that the association of age with survival prospects is to an extent independent of severity, a deduction contrary to that of Russek et al.[208] Whether further refinement in the classification of severity or the subdivision of patients by other relevant categories would eliminate this apparent association and thus make it possible to disregard age in estimating prognosis could not be tested in the present series because of lack of sufficient cases for meaningful rates for the extensive subdivisions required. *Until such refinements can be carried out, it seems wise to take both age and severity at onset into account when estimating survival prospects.*

Good and Poor Risk Status

The evaluation of severity used in the foregoing analysis was made by the attend-

TABLE 133

[illegible] have been Good and Poor Risk Cases by Criteria Approximating Those of Russek *et al.*[208]

Estimate of Risk	Total Cases Observed: Control Group	Total Cases Observed: Treated Group	Percentage of Cases Dying[a]: Control Group[b]	Percentage of Cases Dying[a]: Treated Group
Moderately strict definition of good risk:[c]				
Good risk cases	65	114	1.5	1.8
Poor risk cases	377	475	27.2	19 4
Very strict definition of good risk:[d]				
Good risk cases	24	47	0.0	0.0
Poor risk cases	418	542	24.8	17.3

Note. *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such figures* [illegible]

[illegible] poor risk deaths, 95 (corrected, 102 5) and 92 respectively. By the strict definition, all deaths occurred in the poor risk group (i e , 96, or 103 5, corrected, in the control group and 94 in the treated group).

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[c] See definition on p 231.

[d] Same definition as for moderately strict except that third degree pain was added to the criteria for poor risk.

[**] The difference in percentage dying between control and treated group mildly or moderately ill patients is of "borderline" significance statistically as defined for this study The corresponding difference in the case of severely ill patients was not sufficient to be statistically significant in view of the relatively small groups involved.

ing physician without any instructions as to the criteria by which severity was to be appraised. More definite criteria have since been suggested, however, by Russek et al.[209] These investigators have proposed that myocardial infarction cases be screened on the day of admission for "good" and "poor risk" indications and that only those patients who appear on this basis to be poor risks be given anticoagulant therapy. In view of the importance of the issue thus raised, a poor risk definition approximately equivalent in most respects to that used by Russek et al. was applied to the cases in the present study and the experience with respect to complications and deaths tabulated for the good and poor risk groups thus defined. The details of this experiment, including the criteria used in distinguishing good risk cases, were reported in the chapter on complications (Chapter VIII). The method did not prove sufficiently successful in the present study in predicting complications to warrant recommending its use in determining which myocardial infarction cases should receive anticoagulant therapy. Twenty-three per cent of the good risk control group cases developed thromboembolic complications. These totalled 29 per hundred cases. Hemorrhagic complications developing in good and poor risk cases are discussed in Chapter IX.

The results in the case of deaths, on the other hand, were more favorable to the use of these good risk criteria for prediction. They are reported in Table 133 and Figure 138. In the present study, under the moderately strict definition,[44] only 3 good risk cases died. Two of these three were over 80

[44] For the criteria for this moderately strict definition, see p. 231.

DEATHS IN GOOD AND POOR RISK CASES

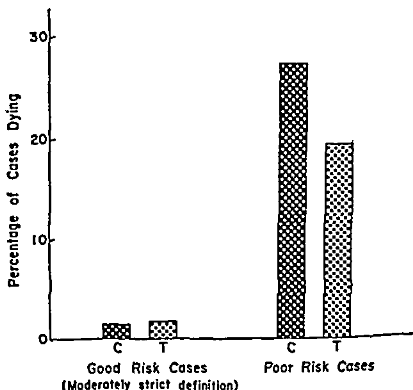


Figure 138. DEATHS IN GOOD AND POOR RISK CASES: Percentage of cases dying in the control and treated groups among patients estimated to have been good and poor risk cases by moderately strict criteria approximating those of Russek et al.[209]

years old. Thus, if an age of 80 or over had been defined as a poor risk criterion, the total would have been reduced to one case. It is also of interest that two of the three good risk cases dying (one control, one treated but treated inadequately) died of an extension of the original infarction. Thus, fatal thromboembolic phenomena do also occur in good risk cases.

Stated in terms of percentage, the proportion dying among good risk cases by the moderately strict definition did not exceed 2 per cent in either the control or the treated group. This rate compares closely with the 3.1 per cent rate reported by Russek et al. for the good risk component of their combined series.[201] It is also approximately similar to rates for mild cases reported by, Littman,[133] Furman et al.,[88] and Papp and Smith.[174] Manchester and Rabkin,[131] on the other hand, reported a somewhat higher fatality rate for good risk cases (4 per cent). In the present study, application to the present sample of a more strict definition of good risk, one which included third degree pain as a poor risk indicator, eliminated all deaths in the good risk group.

On the surface, these data on deaths appear to support the position of Russek et al. that anticoagulants are needed only by poor risk cases. Caution in this deduction is indicated, however, on the following grounds: (1) Since the good risk group in the present study was reduced by this same procedure to excessively small size, the absence of deaths in this particular sample can give no assurance that good risk cases of this type have a true death rate of zero. (2) Since only 17 per cent of the cases in the present series could meet even the criteria specified for moderately good risk cases, omission of anticoagulant therapy for such cases could at most result only in relatively minor savings of time, effort, and expense. (3) Application of such a selection procedure on the basis of the present death findings only would require the assumption that prevention of death was the only objective, whereas it seems eminently important to prevent such developments as pulmonary and cerebral emboli and new myocardial infarctions even though these prove to be nonfatal. *In view of these considerations, the procedure of confining anticoagulant therapy to poor risk cases cannot be recommended in spite of the highly favorable death record of good risk cases.*

Development of Thromboembolic Complications

A third and very obvious method of prognosis with respect to survival would make [illegible] it has been demonstrated (see Chapter VIII) that further thromboembolic phenomena are more probable among those who have already shown one complication than among those who have not, and since each such complication may itself precipitate death, it follows logically that the prognosis for survival is considerably more grave for those who have shown thromboembolic complications than for those who have not. The relationship is almost too obvious to [illegible] quoted are standardized for age.

A striking association between complications and deaths is demonstrated both in the [illegible] diagnosed thromboembolic complication died before the end of six weeks as contrasted with 38 per cent of those for whom one or more complications were diagnosed clinically during their illness. Thus control group patients who developed complications had less than half as good a chance of surviving the illness as did those who never showed a complication.[*] A similar

[*] The true contrast in chances of survival for patients with and without complications is actually greater than here indicated since all deaths are counted for the "no complication" group

ing physician without any instructions as to the criteria by which severity was to be appraised. More definite criteria have since been suggested, however, by Russek et al.[309] These investigators have proposed that myocardial infarction cases be screened on the day of admission for "good" and "poor risk" indications and that only those patients who appear on this basis to be poor risks be given anticoagulant therapy. In view of the importance of the issue thus raised, a poor risk definition approximately equivalent in most respects to that used by Russek et al. was applied to the cases in the present study and the experience with respect to complications and deaths tabulated for the good and poor risk groups thus defined. The details of this experiment, including the criteria used in distinguishing good risk cases, were reported in the chapter on complications (Chapter VIII). The method did not prove sufficiently successful in the present study in predicting complications to warrant recommending its use in determining which myocardial infarction cases should receive anticoagulant therapy. Twenty-three per cent of the good risk control group cases developed thromboembolic complications. These totalled 29 per hundred cases. Hemorrhagic complications developing in good and poor risk cases are discussed in Chapter IX.

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[44] For the criteria for this moderately strict definition, see p. 231.

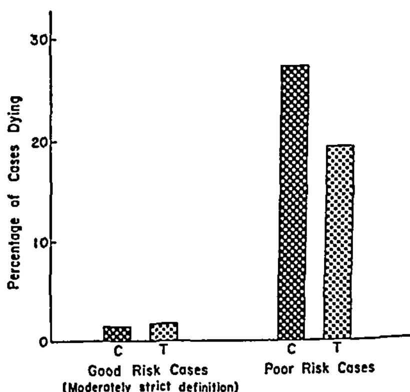


Figure 138. DEATHS IN GOOD AND POOR RISK CASES: *Percentage of cases dying in the control and treated groups among patients estimated to have been good and poor risk cases by moderately strict criteria approximating those of Russek et al.*[309]

ment of a thromboembolic complication following a myocardial infarction is in itself a grave prognostic sign.

Further inspection of the findings indicates that the major savings in total deaths achieved with anticoagulants resulted not from an improved chance of survival within the component groups as here defined, but rather from the retention in the "no complication" component of the treated group of 89 per cent of the total cases in that group instead of 74 per cent, as in the control group. Since the purpose of giving anticoagulants is the prevention of thromboembolic complications, this result would be expected.

The unexpected feature of Figure 139 is rather the fact that minor differences in fatality rates in favor of the treated group remained even after the control and treated groups were equated in terms of the presence or absence of complications. Since these residual differences are not statistically significant at the significance level adopted for this study, a chance explanation of these differences cannot be disproved. The existence of a residual difference in both subgroups offers nevertheless a temptation to speculation. If not due to chance, the residual difference may result from the prevention of complications in the treated group of the types often evading clinical diagnosis but nevertheless capable of affecting survival prospects. The data on the autopsy findings demonstrate that such failures in diagnosis are frequent occurrences For the subgroup [illegible] those in the treated group who developed one complication showed fewer subsequent complications than the corresponding component of the control group (see Chapter VIII).[a]

[a] Because of the small number of cases showing more than one complication, a breakdown of death rates according to the number of prior complications is not presented

Thus, once more, the favorable influence of anticoagulants demonstrates itself in hidden, subtle ways as well as in the expected fashion.

Location of Infarction

To explore further the possibilities of survival prognosis from information available at the outset of the illness, deaths were also tabulated by the location of the original infarction. The results are shown in Table 135, Appendix F Table 70, and Figure 140. In both the control and treated groups the percentage dying was found slightly higher among those with anterior, anterolateral, and anteroseptal infarctions than among those with posterior, posterolateral, and posteroseptal infarctions. Though the pattern was consistent, the differences were

TABLE 135

DEATHS IN RELATION TO LOCATION OF ORIGINAL [illegible]

Location of Original Infarction	Total Cases Observed		Percentage of Cases Dying (Rates Standardized for Age)[a]	
	Control Group	Treated Group	Control Group[b]	Treated Group
Anterior infarction[c]	231	319	23.9	15.8
Posterior infarction[d]	171	211	20.9	12.0
All other types[e]	40	59	32.3[f]	33.9[f]

[a] For explanation of process of standardization, see footnote a, Table 101.

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

[c] Includes anterior, anterolateral, and anteroseptal infarctions

[d] Includes posterior, posterolateral, and posteroseptal infarctions

[e] Includes septal infarctions, infarctions characterized by diffuse changes, and infarctions whose site is obscure or unknown, and multiple infarctions at onset.

[f] Rates for this subgroup could not be standardized for age because of the small number and mixed character of the cases in this category.

TABLE 134

DEATHS IN RELATION TO PRESENCE OR ABSENCE OF THROMBOEMBOLIC COMPLICATIONS: Percentage of Cases Dying in the Control and Treated Groups among Patients Developing One or More Thromboembolic Complications and among Patients Developing No Thromboembolic Complications during the Six-Week Period of the Illness

Status of Thromboembolic Complications during the Illness	Total Cases Observed		Percentage of Cases Dying (Rates Standardized for Age)[a]	
	Control Group	Treated Group	Control Group[b]	Treated Group
No thromboembolic complications	327	525	18.0	13.9
One or more thromboembolic complications. .	115	64	37.5	34.1

[a] For explanation of process of standardization, see footnote a, Table 101.

[b] Data are corrected for exceptions in treatment. For method of correction, see Appendix B.

contrast was evident in the treated group. Only 14 per cent of those with no complications died as compared with 34 per cent of those with one or more complications. The difference is statistically significant in the control group and highly significant in the treated group. Mintz and Katz[112] have also noted a similar relationship between complications and deaths. In their series of 572 patients, 52 developed thromboembolic complications. The mortality among these patients was 55.8 per cent as compared with a rate of 21.8 per cent for their entire group. Thus *there can be little doubt that the develop-*

whereas only deaths after a thromboembolic complication could, by definition, be counted for the "one or more complication" group (since membership in this group had to await the development of a complication). A more precise evaluation of chances would require the computation of an artificial death rate for the "no complication" group for a period of the illness comparable to that observed for the group with complications.

DEATHS IN RELATION TO THROMBOEMBOLIC COMPLICATIONS

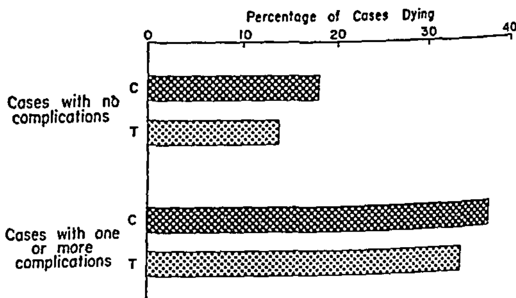


Figure 139. DEATHS IN RELATION TO THROMBOEMBOLIC COMPLICATIONS. Percentage of cases dying in the control and treated groups among patients who did and did not develop one or more thromboembolic complications during the illness (rates standardized for age).

nfarctions, showed higher death rates than either the anterior or posterior infarction groups, and no improvement with anticoagulants was evident. Detailed counts for component groups of the "all other" category appear in Appendix F, Table 70. Because of the small size and mixed character of this residual group, judgment must be deferred both regarding the correctness of the seemingly poor prognosis associated with septal infarctions and diffuse and obscure changes and regarding the benefits of anticoagulant therapy with this group. Until these relationships have been clarified, the findings of the present study should *not* be considered grounds for withholding anticoagulant therapy from patients of these types.

Abnormal Rhythms

Abnormal rhythms during the first week were also tabulated in relation to deaths in the belief that such abnormalities might likewise have prognostic value. The same rhythm categories were used as in previous tabulations on this topic, but only the more frequent types were present in sufficient numbers to provide a base for meaningful rates. The findings are shown in Table 136, Appendix F Table 71, and Figure 141

The presence of arrhythmias in the first week appears to have decided prognostic value. In the control group a third of the patients showing abnormal rhythms of any type died within six weeks as contrasted with only about a sixth of those for whom no arrhythmias were reported. The contrast between corresponding components of the treated group ...

ately. I...

highly ...

also in accord with other clinical experience.[33, 35] Marked improvements in death rates were associated with anticoagulant therapy in both major groups, but the favorable contrast was greater among those without any abnormal rhythms in the first week than among those showing rhythm deviations

Of the specific arrhythmias for which rates were calculated, the most unfavorable survival prospects for control group patients were found for auricular fibrillation and for the general category, heart block. The percentage dying in the control group exceeded forty per cent in both these categories. When the heart block group was restricted, by the elimination of the A-V block cases, to those showing left or right bundle branch block only, the record for this group was less ominous, but since the sample was then

TABLE 136

DEATHS IN RELATION TO ABNORMAL RHYTHMS Percentage of Cases Dying in the Control and Treated Groups among Patients Who Showed Various Types of Abnormal Rhythms during the First Week of the Illness

Type of Abnormal Rhythm	Total Cases Observed[a]		Percentage of Cases Dying[b]	
	Control Group	Treated Group	Control Group[c]	Treated Group
Specific types of abnormal rhythms:[d]				
Auricular fibrillation	30	39	42.7	*23.2*
Heart block of any type or degree	43	60	40 2	35.0
Left or right bundle branch block	20	47	*27.0*	31 9
Premature contractions, ectopic beats or extrasystoles	64	82	23 6	20.7
Any type of abnormal rhythm[e]	162	204	33.3	25.0
No abnormal rhythm	271	378	17.1	10.6

Note *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such rates particularly unstable.*

[a] No report on abnormal rhythms was available for 9 cases in the control group and 7 cases in the treated group

[b] Rates are not standardized for age.

[c] Data are corrected for exceptions in treatment. For method of correction, see Appendix B

[d] Types of rhythms other than those listed were found in too small numbers to form an adequate basis for rates

[e] Includes any abnormality recorded by the reporting physician as a rhythm abnormality in item 47 of the schedule, including many types of abnormal rhythms not listed above.

relatively slight, too slight to be statistically significant for samples of these sizes. The data also yield no clues as to a physiological explanation, if any, of this difference, and the explanation is otherwise not obvious.

This lack of a marked and clearly significant difference in mortality in relation to the location of the original infarction is consistent with the lack of agreement on this same point among other investigators. Vander Veer and Brown,[235] and Wood et al.[245] and others[116] have stated that an anterior infarction is considerably more serious than a posterior infarction. Yater et al.[265] also believe that their data support the view that occlusion of the left anterior descending coronary artery is more serious than occlusion of the right coronary artery. On the other hand, Master, Jaffe, and Dack,[142] Willius,[248] Barnes and Ball,[13] Mintz and Katz,[152] and Levine and Brown[115] have reported that there is little difference in the mortality rates for anterior and posterior infarctions. The issue, therefore, is not resolved by the findings of other investigators.

A return to Figure 140 indicates further that marked improvements were associated with anticoagulant therapy in both the anterior and posterior infarction groups. *One can reasonably conclude, therefore, that anticoagulant therapy is beneficial for both groups.* Improvement was slightly greater in the posterior infarction than in the anterior infarction group but the difference was not such as to justify a differentiation in therapy.

In both the control and treated groups, the "all other" group, composed of patients with septal infarctions, infarctions characterized by diffuse changes, infarctions of obscure and unknown site, and multiple

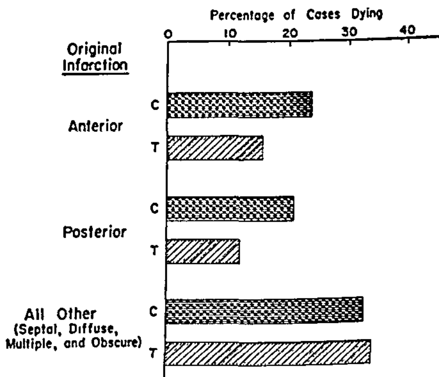


Figure 140. DEATHS BY LOCATION OF ORIGINAL INFARCTION: Percentage of cases dying among patients in the control and treated groups having single original infarctions of an anterior or posterior location (rates standardized for age) and among patients having original infarctions of other types (as defined in footnote e, Table 135).

Congestive Heart Failure and Shock

As a final step in the analysis, fatal cases were tabulated in relation to the presence or absence of congestive failure and/or shock during the first two days and in later weeks. Table 137 presents the percentage of cases [illegible] and not showing [illegible]

[illegible] who survived to the beginning of the second week and did or did not show heart failure and/or shock after the first week. The major findings in both these tables appear in Figure 142. Actual counts for various small subgroups are given in Appendix F, Tables 72 and 73. Some detail as to week of death is also given in Appendix F Table 72.

Initial heart failure or initial shock were common in the early days of the illness, occurring to some degree in about a third of the cases studied. Since these syndromes cleared rapidly in many cases, they had less prognostic significance than did the presence of heart failure and/or shock after the first week. *Nevertheless*, in both treatment groups, the fatality rates associated with

TABLE 137

DEATHS IN RELATION TO INITIAL CONGESTIVE HEART FAILURE AND SHOCK: Percentage of Cases Dying in the Control and Treated Groups during the Total Six-Week Period of the Illness among Patients with Initial Congestive Heart Failure and/or Shock, or Neither of These Conditions

Status of Initial Congestive Heart Failure and Shock[a]	Total Cases Observed		Percentage of Cases Dying[b]	
	Control Group	Treated Group	Control Group	Treated Group
Initial heart failure present	107[d]	112[e]	30 9	30 4
Initial shock present	85[d]	120[e]	30.4	25.8
Either initial heart failure or initial shock or both present ...	161	195	29 2	25 1
Neither initial heart failure nor initial shock present.	281	334	20.1	11.4

[a] Counts include only those cases for whom the reports of heart failure or shock symptoms were sufficiently definite to make clear that they occurred during the first two days They include cases with mild as well as severe symptoms, cases whose heart failure symptoms began prior to the initial attack, and cases in which hepatomegalia was the only symptom of heart failure.

[b] Data are not standardized for age

[c] Data are corrected for exceptions in treatment. For method of correction, see Appendix B

[d] Includes 31 control group cases showing both initial heart failure and shock.

[e] Includes 37 treated group cases showing both initial heart failure and shock.

TABLE 138

DEATHS IN RELATION TO CONGESTIVE HEART FAILURE AND SHOCK AFTER THE FIRST WEEK: Percentage of Cases Dying in the Control and Treated Groups among Patients Who Survived to the Beginning of the Second Week and Showed Congestive Heart Failure and/or Shock, or Neither, after the First Week

Status of Congestive Heart Failure[a] and Shock after the First Week	Total Cases Surviving at Beginning of Second Week		Percentage of Cases Surviving at Beginning of Second Week Dying Second through Sixth Week[b]	
	Control Group	Treated Group	Control Group[c]	Treated Group
Heart failure present	88[d]	97[e]	41.7	33.0
Shock present	23[d]	19[e]	*71.3*	*63.2*
Either heart failure or shock or both present	93	104	44.0	32.7
Neither heart failure nor shock present ..	312	445	8.8	4.5

Note: *Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Includes both left and right heart failure, cases with either mild or severe symptoms, and cases with hepatomegalia only.

[b] Based on total cases surviving to beginning of second week, corrected for exceptions in treatment in the control group, showing given symptoms after first week. (See footnote b, Appendix F Table 73.) Data are not standardized for age.

[c] Data are corrected for exceptions in treatment For method of correction, see Appendix B.

[d] Includes 13 cases showing both heart failure and shock.

[e] Includes 12 cases showing both heart failure and shock.

reduced to 20 cases, this lower rate may be due to chance. Control group patients with premature contractions, ectopic beats, and extrasystoles, on the other hand, showed a death rate about as favorable as that for the control group as a whole but definitely less favorable than that for patients with no arrhythmias. If these findings are typical, *these arrhythmias may be presumed the least serious of those tabulated.*

Survival prospects for those with the various arrhythmias showed the same rank order in the treated as in the control group, provided one omits auricular fibrillation cases which dropped from first to third rank in the percentage of deaths. This drop for auricular fibrillation is consistent with the favorable thromboembolic complication record previously reported in Chapter VIII for cases of this type when treated with anticoagulants. Of the three remaining rhythm abnormalities, two showed only a slight reduction in deaths in the treated group as compared with the control group, while the third (left and right bundle branch block) showed a reversal of direction, the treated group fatality rate being higher than the control group rate. Since the control group component contained only 20 cases, this change in direction may reasonably be attributed to chance. It is clear, however, that when these serious abnormalities are present early in the illness, survival prospects remain poor even though anticoagulants are used and succeed in preventing complications.

Because of the small sample available, ventricular fibrillation was not included in Table 136, or Appendix F, Table 71. This extremely serious abnormality of rhythm occurred in the first week in 2 control and 4 treated group cases, all of whom died. Since this arrhythmia is usually a terminal phenomenon, this one hundred per cent fatality rate may be considered typical in spite of the small number of cases on which it is based

DEATHS IN RELATION TO ABNORMAL RHYTHMS

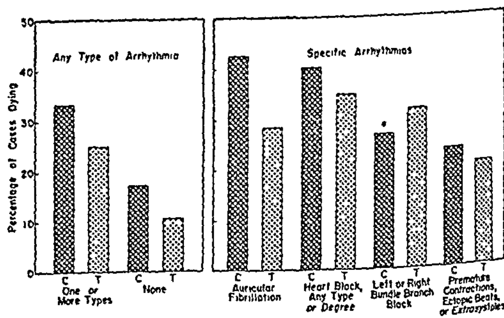


Figure 141. DEATHS IN RELATION TO ABNORMAL RHYTHMS: Percentage of cases dying in the control and treated groups among patients who showed various types of abnormal rhythms, any type of abnormal rhythm, and no abnormal rhythms during the first week of their illness.

hese unfavorable survival prospects also substantiate the conclusions of Mintz and Katz[113] *that congestive failure is an extremely grave prognostic sign in patients with coronary occlusion with myocardial infarction. These* investigators have reported an immediate mortality in such cases of 41.9 per cent, a figure that is remarkably close to the 41.7 per cent mortality reported in Table 138 for control group cases in the present series showing heart failure after the first week.*

As is well recognized, the exact cause of death in such states is often difficult or impossible to determine even at autopsy. In this series, the data presented do not indicate whether congestive failure or shock was, or was not, the primary or final cause of death for these patients. In some instances these syndromes represented subsequent reactions to other conditions, as, for example, a large original infarction or a subsequent thromboembolic complication. In other instances, the circulatory stasis associated with congestive heart failure or shock probably contribute to the development of subsequent thromboembolic complications (see page 249), which in turn prove fatal. In still other patients, these syndromes merely reflected a moribund condition precipitated by other underlying pathological states

This picture may be amplified somewhat with data from Master, Dack, and Jaffe since these investigators did analyze their series from the point of view of the role of congestive heart failure in producing death[1??] They believed congestive heart failure to be the chief cause of death among myocardial infarction patients 50 or more years of age and arterial embolism, the chief cause for patients under 50.

The data in Tables 137 and 138 can also be re-examined in relation to a second question, namely: Do anticoagulants improve the prospects of survival when congestive failure and shock are present? In all categories shown in Figure 142, regardless of the period concerned, the treated group showed lower rates than the control group. In the case of initial heart failure and/or shock, the differences were very slight and essentially disappeared when cases with initial shock only were eliminated from the classification. This similarity may or may not signify an absence of savings from anticoagulants in such cases.

Of the control group cases showing congestive heart failure and/or shock after the first week, 44 per cent died before the end of the study period as compared with 33 per cent in the treated group. While the contrast in this instance is suggestive of some savings in lives due to anticoagulants, the samples are again too small to permit the difference to be termed "statistically significant" at the significance level adopted for this study. This difference was, however, consistent with the findings of Griffith et al.,[77] Harvey and Finch,[88] and Anderson and Hull[4] for congestive failure series that utilized control groups. Each of these authors has reported very substantial reductions in mortality in congestive failure cases when anticoagulants were administered. Conclusions from the present series must, nevertheless, be restrained. *It seems appropriate to conclude, therefore, that the favorable consequences of anticoagulant therapy in congestive heart failure and shock were clearly apparent when thromboembolic complications were the measure used* (see Chapter VIII), *but while still apparent when deaths are used as the test of effectiveness, the favorable trend is less conspicuous and cannot be asserted with the same degree of confidence until larger samples become available.* This difficulty in demonstrating a statistically significant difference in the case of deaths in the small group of cases with continuing heart failure and shock was to be expected since in many such cases a fatal outcome may be inherent in the seriousness of the original infarction and may be unavoidable regardless of therapy. *Nothing in the death findings suggests that the outlook for*

* The exact correspondence is, no doubt, a chance coincidence since classification procedures were probably not fully comparable.

these syndromes were higher than those for patients without these conditions. Among patients in the control group with either initial heart failure or shock, 29 per cent died; among those with neither, 20 per cent. For those in corresponding categories of the treated group, the percentages dying were 25 per cent and 11 per cent respectively. The prospects for survival were about the same for control group patients with initial heart failure as for those with initial shock. In the treated group, they were also fairly similar.

When heart failure or shock persisted into the second and later weeks, or developed then for the first time, the outlook for survival became considerably less favorable. The prognosis for those with shock after the first week was particularly grave. Among the small group of control cases showing shock during this later period (23 cases), more than 70 per cent died. This finding is in agreement with the experience reported by Mintz and Katz[1**] that among 36 of their myocardial infarction patients exhibiting definite signs, symptoms and blood pressure changes indicative of shock, 78 per cent died (as contrasted with 20 per cent of their normotensive patients and 23 per cent of their hypertensive patients). Levine and Brown[114] and Master, Dack and Jaffe[113] also agree regarding the poor prognosis associated with shock. It should be noted that in the present study this extremely poor prognosis was characteristic only of shock *after the first week*. Initial shock often clears rapidly and has a much less grave import.

Among the larger group with either heart failure or shock or both in later weeks, deaths exceeded 40 per cent in the control group and 30 per cent in the treated group

DEATHS IN RELATION TO CONGESTIVE HEART FAILURE AND SHOCK

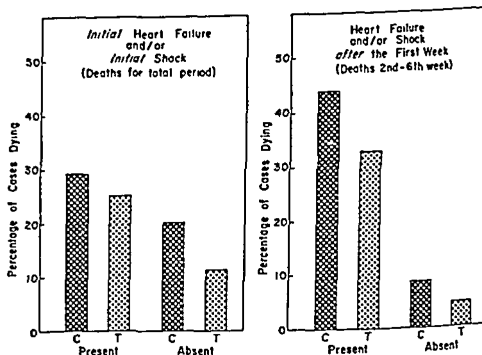


Figure 142. DEATHS IN RELATION TO CONGESTIVE HEART FAILURE AND SHOCK: Percentage of cases dying in the control and treated groups *during the six-week* period of the illness among patients with and without initial congestive heart failure and/or shock and percentage of cases dying from the second through the sixth week among patients in the control and treated groups surviving *to the beginning* of the second week and experiencing congestive heart failure and/or shock or neither, after the first week.

the sample studied was not chosen at random from all hospitals throughout the United States, and cannot therefore be used to describe all hospitalized myocardial infarction cases with any known degree of confidence, examination of the *records for* deaths in other similar series indicates that the present control group took an intermediate position with respect to its death rate, its actual death rate (23.4 per cent) being somewhat below the death rate based on total data from 20 other controlled studies when pooled (i e., 29.5 per cent). It is therefore not extreme with respect to its losses through death. In view of the demonstrated high risk of death that myocardial infarction involves, any therapy that offers promise of reducing fatalities should be used if the procedure is at all feasible and does not involve undue hazards.

This chapter has shown in the second place that the risk of death can be reduced by the administration of anticoagulants. The evidence for this assertion can be summarized as follows:[11]

1. Only about two-thirds as many patients per hundred in the treated as in the control group died within the period of observation (23 4 per cent, control, *vs.* 16.0 per cent, treated). There is no known difference between the groups which would explain a difference of this magnitude.

2. The reduction in deaths appears to have occurred primarily as a result of the prevention of thromboembolic complications with a fatal outcome since 42 per cent of the control group but only 23 per cent of the treated group deaths were preceded by a clinically diagnosed thromboembolic complication.

3 The contrast in the death rate was confined to the period of effective anticoagulant therapy, namely, the period from the fourth day of anticoagulants through four days after the last dose. (Nine and five-tenths per cent of the treated group who began this period died during the therapy period. This is to be contrasted with a 17.4 per cent fatality rate for the control group during corresponding days of their illness.) Deaths in the control and treated groups during the remainder of the six-week period of observation differed only in minor and insignificant ways.

4. This observation is further confirmed by an analysis of deaths by week of illness. The contrasts in death rates were greatest during the second, third, and fourth weeks when coverage by anticoagulants was most complete, and least during the first, fifth, and sixth weeks when coverage by anticoagulants was usually incomplete or absent.

Thus the evidence throughout is consistent with the conclusion that the reduction in deaths was due primarily to anticoagulant therapy and not to any difference between the two groups. Moreover, except as noted, significance tests applied to the findings (1) through (3) above typically gave a verdict of either "significant" or "borderline" in significance.

A review of 21 other controlled studies of the use of anticoagulants in myocardial infarction revealed a difference favorable to anticoagulants in 19, a tie in one, and only one reversal, the latter occurring in a series in which comparability was in doubt. When the observations from this study are combined with those from these 21 other controlled studies, the cumulative evidence in favor of anticoagulants leaves little room for an explanation of the difference in deaths in terms of chance.

The data serve in the third place to delineate the types of patients for whom the mortality risk is relatively high, namely:

1. Those 60 or over and especially those 70 or over.

2. Those 10 per cent or more overweight.

3. Ward patients (i.e., those unable to pay for private or semiprivate care).

4. Those with a history of congestive

[11] Control group rates quoted in this summary have been corrected throughout for exceptions in treatment.

survival of patients with congestive heart failure or shock is adversely affected by anticoagulant therapy.

A favorable association with anticoagulant therapy was more conspicuous in the case of patients with neither congestive failure nor shock. In both Tables 137 and 138, treated group fatality rates for those without either syndrome were only a little more than half as high as those for corresponding control group components. Since both the differences and the groups involved were large, it is quite improbable that they were due to chance.[hh] *The saving of lives associated with anticoagulant therapy in myocardial infarction cases not showing congestive heart failure or shock during their illness thus appears real and perhaps substantial.*

Other Clinical Observations

The chapter on signs, symptoms and laboratory findings during the illness presented extensive data both in tabular and graphic form on the blood pressure, temperature, pulse, and leukocyte count maximums found in fatal and nonfatal cases. These findings are also relevant to the possibility of predicting survival from observations early in the illness. A summary listing of the maximums previously reported as indicative of a grave prognosis is, therefore, included here even though some repetition is involved. The maximums with particularly grave implications were as follows:

1. Leukocyte counts of 20,000 cells per cubic millimeter or more.

2. Maximum rectal temperatures of 103 degrees Fahrenheit or more in the first week.

3. Maximum drops in blood pressure during the first week of 60 mm. systolic or 40 mm. diastolic or more below the usual level prior to the illness.

4. Maximum pulse rates in the first week of 120 beats per minute or more.

5. Maximum NPN readings of 50 or more or maximum BUN readings of 25 or more any time during the illness.

Fatalities for those showing lesser maximum levels for these same observations were, with minor exceptions, also consistent with this pattern. Groups with moderately high maximums in general showed death rates between the extremes while patients with the lowest maximums showed the best survival records. Temperature, blood pressure, and pulse maximums during the second through the sixth week were also tabulated in relation to deaths and likewise found to repeat this same pattern. *Observations of these types thus have definite prognostic value.* Within each of the major categories used in these tabulations, the record for deaths among patients treated with anticoagulants was, with minor exceptions, also consistently more favorable than that of corresponding control groups.

SUMMARY AND CONCLUSIONS REGARDING DEATHS

The data in the present chapter can, in summary, be used for several purposes. *In the first place, they indicate that myocardial infarction involves a serious threat to life.* The average control group patient in this study who survived the first day of hospitalization had slightly more than three chances in four of surviving to the end of the sixth week. Deaths were highest in the first two weeks, but continued at a substantial level through the fourth week. If all cases dying prior to hospitalization or during the first 24 hours had been included, these survival rates would have been even less favorable. While

[hh] The observed differences between treatment groups in the percentage dying among patients with neither initial heart failure nor initial shock would be expected on a chance basis not much more than once in 100 samples. A difference as great as that between treatment groups for cases without any congestive heart failure or shock after the first week would be expected on a chance basis in about 6 in 100 samples. These probabilities were computed on rates before corrections for exceptions in treatment (the usual procedure). Allowance for corrections, would, of course, increase the significance levels.

r more adverse signs would die, and (2) hat "good risk" patients would not develop complications. *The procedure of limiting anticoagulant therapy to "poor risk" cases cannot, therefore, be recommended*

Finally, the data from this chapter can be used to supplement that on complications in determining whether anticoagulants were beneficial with all types of patients. When the fatality record in the treated as compared with the control group was examined from this viewpoint, it was found to show a remarkably consistent record of improvement within subgroups. With certain exceptions,[ii] all fatality rates for subgroups of the treated group based on the total period or the first week ranged from 48 to 88 per cent of the rates for corresponding subgroups of the control group (after the exexclusion of comparisons involving rates based on less than 30 cases).

This consistency is demonstrated graphically in Figure 143, which summarizes the case fatality rates for 20 of the major subgroups studied. The method of graphic portrayal is the same as that previously used for thromboembolic complications in Figure 107, Chapter VIII. In order that lines representing similar percentage reductions below the control group levels for specific types of patients may show a similar slant regardless of the absolute levels of rates, a logarithmic scale is used. Rates for the control group appear as dots to the left of each section under the heading "C" (with an arrow) and are connected with lines to dots for treated group rates for the same types of patients that appear on the right of each section below the "T" (with an arrow). Each of the five sections contains two pairs of lines, one solid and one broken, each pair of similar lines representing a dichotomous classification of cases according to some specific characteristic identified in the legend at the bottom on the same section. In comparison with the corresponding figure for thromboembolic complications (Figure 107), it is clear that there is greater diversity in the relative levels of deaths by type of patient and the improvements associated with anticoagulant therapy are less consistent percentagewise and less dramatic in the amount of the drop[kk]—differences that might be expected from the indirect and often indecisive relationship between anticoagulants and death. Nevertheless, a certain general similarity in slope prevails and all groups except one show a more favorable death record with than without anticoagulant therapy. This single reversal, that for good risk cases, is insignificant (control, 1.5 per cent; treated, 1.8 per cent) and appears important only because at this point the logarithmic scale exaggerates small differences. With a more

[ii] The exceptions were (1) patients 50 to 59 years of age, (2) patients with initial [illegible] previous infarctions prior to the attack, (8) patients with a maximum temperature below 101 degrees Fahrenheit during the first week, and (9) cases with miscellaneous types of infarction (i e, septal, diffuse, multiple) In only the last four categories listed was the treated group rate higher than the control group rate and in three of these instances differences were always below three percentile points The reversal in subgroup (7) actually only occurred in the ward cases in this subgroup (see p. 323) In subgroup (9) the absence of a reduction in treated group deaths with these patients is inconclusive because of the small and mixed character of this subgroup In three of the four subcategories in which reversals in the fatality rates occurred, the percentage of cases developing complications was less than half as high in the treated as in the control group A total of 54 subgroups were compared, namely, all that were available for the first week or total period that included more than 30 cases in both the control and treated groups. (Comparisons are not independent since the same cases reappear several times, reclassified by varying characteristics)

[kk] Part of the seeming difference in slant is due to the smaller scale used in the present figure, a difference made in adjustment to the greater spread in rate levels.

failure, diabetes, arteriosclerosis, or hypertension prior to the attack.

5. Those evaluated by their attending physician as severely ill at onset or as poor risks (Russek's[209] criteria).

6. Those showing abnormal rhythms during the first week, especially auricular fibrillation and heart block.

7. Those who develop a thromboembolic complication.

8. Those with leukocyte counts of 20,000 cells per cubic millimeter or more in the first week.

9. Those with maximum rectal temperatures of 103 degrees Fahrenheit or more at some time during the first week.

10. Those with maximum drops in blood pressure during the first week of either 60 mm. systolic or 40 mm. diastolic below their usual level prior to the illness.

11. Those with a maximum pulse rate in the first week of 120 or over.

12. Those with maximum NPN readings of 50 or more or maximum BUN readings of 25 or more anytime during the illness.

13. Those showing initial congestive heart failure or shock.

14. Those showing persistent heart failure or shock or developing these syndromes after the first week.

The patterns in these respects were generally similar in both the control and treated groups, though contrasts were often smaller within the treated than within the control group. This consistency, plus the reasonableness of the observed relationships, suggests that the foregoing deductions are valid even though, with the samples available for some subgroups, their explanation in terms of chance could not always be ruled out at the adopted level of significance.

Since the existence of these various characteristics usually becomes known early in the illness, they can provide definite guidance in estimating the probability that the patient will survive the attack. They should also be considered evidence that the patient has more than the usual need for anticoagulant protection because of his otherwise precarious status.

The following other characteristics could not be demonstrated in the present series to have any conspicuously positive or statistically significant association with a high fatality rate (after standardization for age): (1) the sex of the patient, (2) the anterior or posterior location of the infarction, (3) a history of coronary artery disease or anginal syndrome. If the picture these data present is a true one, these characteristics do not in themselves have significant prognostic import. However, with a larger sample a significant difference in some of these categories might be demonstrated. A difference in deaths associated with premature contractions, extrasystoles, and ectopic beats early in the illness was present but was minor when compared with the more serious arrhythmias. Evidence regarding the effect of a previous infarction on the outlook for survival from subsequent infarctions was inconclusive.

Since the various characteristics of any given patient are obviously neither fully independent nor of equal importance, the gravity of the prognosis for a given patient is not directly proportional to the number of adverse signs that he shows. Some composite weighted appraisal of these traits would therefore be appropriate in evaluating the prospects for individual patients. In the present study, no attempt was made to develop a systematic quantitative method for weighting these various criteria. A simpler type of combined appraisal was attempted, however. Following the procedure developed by Russek et al.,[209] the sample was divided into "good" and "poor risk" cases, the "poor risk" cases being any that demonstrated in the initial stages of the illness, certain adverse signs. The procedure was found to be reasonably successful in predicting that a certain few cases with no unfavorable signs whatsoever would survive the attack. It was definitely not successful in predicting (1) which patients with one or

the initial attack, the presence or absence of protection from thromboembolic phenomena can be at most only one of the factors determining the outcome.

For patients for whom the risk of death was extremely low, namely, the "good risk" cases, improvement in the death record could hardly be expected. Control group cases in this subgroup experienced the impact of a total of 18 thromboembolic complications with only one death, a death rate below 2 per cent and similar to that for the treated group "good risk" cases.

This mixed pattern with respect to the extent to which anticoagulant therapy was associated with a reduced death rate reflects the complexities and indirectness of the relationship between anticoagulant therapy and ultimate death. The patient's condition prior to the attack, the seriousness of the attack itself, the existence of physiological conditions *favoring or discouraging* the thromboembolic *process, the patient's* capacity to rally after a complication, and chance factors all confuse the picture. Nevertheless, with remarkable consistency, comparisons have reflected some underlying margin of savings in lives.[ll] While the savings were typically of lesser magnitude than in the case of *counts* for thromboembolic complications, they concerned the more [illegible]

The consistency of this favorable differential makes possible two further conclusions: (1) the presence of some difference in the overall death rate associated with anticoagulant therapy cannot be attributed to any possible bias in the sampling process since any reasonable system for reweighting the components that could be conceived of, while it could alter the amount of the observed difference, could not eliminate it entirely.[mm] (2) Practically all types of patients that could be identified in the present series appeared to have benefited to some extent from anticoagulant therapy. Most types benefited by a reduction in deaths. *The "good risk"* group and the other three *categories that* did not show a reduction in *deaths* nevertheless showed substantial re*ductions in the* risk of complications.[nn] The authors *therefore* conclude that among myocardial infarction patients who survive long enough for hospitalization and diagnosis, *no type has thus far been identified in this study that should be excluded from anticoagulant therapy on the grounds that such patients have no potential chance of benefiting from such therapy.* The only medical grounds for excluding such patients from anticoagulant protection would appear to be the chance that they may be harmed thereby either (1) because contraindications point in specific cases to an excessive risk of hemorrhage, or (2) because adequate medical or laboratory safeguards for the proper administration of anticoagulants are unavailable.

[illegible] differences could not always be demonstrated to be statistically significant. This fact does not prove, however, that there was [illegible] real benefit [illegible] in the [illegible] most [illegible] same [illegible] for any given component without further careful study

[mm] A change in the amount of the difference would alter, however, the probabilities found on significance tests and hence the significance level for conclusions.

[nn] See footnote ii, p 345, and pp. 223-225.

strict definition of good risk cases, no deaths were found in either group regardless of the therapy used.

A closer examination of Figure 143, together with rates for other subgroups not shown graphically, reveals that differences in deaths that were favorable to anticoagulants were particularly dramatic in patients of the following selected types: (1) patients 10 per cent or more overweight, (2) patients with diabetes, (3) patients with auricular fibrillation in the first week, and (4) patients 60 years of age and over. Conspicuous differences also occurred among those not otherwise particularly threatened by the attack, as for example, among (1) patients evaluated by their attending physician as mildly or moderately ill at onset, (2) patients showing no congestive heart failure or shock, and (3) patients with no abnormal rhythms in the first week. Probably thromboembolic complications constituted the major hazard for such patients, with the result that the effects of anticoagulant therapy were clearly reflected in the death counts.

At the opposite extreme, other types of patients showed minimal improvement under anticoagulants in the percentage dying, as for example, patients with initial heart failure without shock, or those with a history of heart failure. Some obviously severely threatened groups showed, however, substantial improvement, as for example, patients with auricular fibrillation in the first week and those with heart failure or shock after the first week. For others, such as those with heart block in the first week, the observed reduction was less dramatic. Since chance and uncontrolled inequalities in subgroups enter into these comparative results, conclusions as to differences in subgroup effects must be guarded. It is obvious, however, that in cases severely threatened by

Figure 143. CASES DYING SUMMARIZED BY SUBCLASSES: Percentage of cases dying in the control and treated groups contrasted by various subclasses on a logarithmic scale. (For definitions, see pp. 318–342.)

the initial attack, the presence or absence of protection from thromboembolic phenomena can be at most only one of the factors determining the outcome.

For patients for whom the risk of death was extremely low, namely, the "good risk" cases, improvement in the death record could hardly be expected. Control group cases in this subgroup experienced the impact of a total of 18 thromboembolic complications with only one death, a death rate below 2 per cent and similar to that for the treated group "good risk" cases.

This mixed pattern with respect to the extent to which anticoagulant therapy was associated with a reduced death rate reflects the complexities and indirectness of the relationship between anticoagulant therapy and ultimate death. The patient's condition prior to the attack, the seriousness of the attack itself, the existence of physiological conditions favoring or discouraging the thromboembolic process, the patient's capacity to rally after a complication, and chance factors all confuse the picture. Nevertheless, with remarkable consistency, comparisons have reflected some underlying margin of savings in lives.[ll] While the savings were typically of lesser magnitude than in the case of counts for thromboembolic complications, they concerned the more crucial question of survival.

[ll] When subgroups were small in size or differences were small, differences could not always be demonstrated to be statistically significant. This fact does not prove, however, that there was no real benefit associated with anticoagulant therapy in these subgroups In view of the consistency of most of the differences it would not be safe to assume a lack of difference for any given component without further careful study

The consistency of this favorable differential makes possible two further conclusions: (1) the presence of some difference in the overall death rate associated with anticoagulant therapy cannot be attributed to any possible bias in the sampling process since any reasonable system for reweighting the components that could be conceived of, while it could alter the amount of the observed difference, could not eliminate it entirely.[mm] (2) Practically all types of patients that could be identified in the present series appeared to have benefited to some extent from anticoagulant therapy. Most types benefited by a reduction in deaths. The "good risk" group and the other three categories that did not show a reduction in deaths nevertheless showed substantial reductions in the risk of complications.[nn] The authors therefore conclude that among myocardial infarction patients who survive long enough for hospitalization and diagnosis, *no type has thus far been identified in this study that should be excluded from anticoagulant therapy on the grounds that such patients have no potential chance of benefiting from such therapy.* The only medical grounds for excluding such patients from anticoagulant protection would appear to be the chance that they may be harmed thereby either (1) because contraindications point in specific cases to an excessive risk of hemorrhage, or (2) because adequate medical or laboratory safeguards for the proper administration of anticoagulants are unavailable.

[mm] A change in the amount of the difference would alter, however, the probabilities found on significance tests and hence the significance level for conclusions.

[nn] See footnote jj, p 345, and pp. 233-235

CHAPTER XII

Prothrombin Times in the Control of Anticoagulant Therapy

STATISTICAL analyses of the prothrombin times reported for the patients included in this study are utilized in the present chapter to clarify, insofar as feasible, a number of related questions of interest, notably the following:

1. The variation among hospitals in the meaning of prothrombin times expressed in seconds.
2. The definition of the optimum therapeutic range within which the risk of both thromboembolic complications and hemorrhages is minimized.
3. The extent to which the incidence of thromboembolic complications can be reduced by consistency in prothrombin level control and other characteristics of relatively ideal therapy.
4. The extent to which the rates reported for the present study represent those associated with optimal control procedures.
5. The speed and duration of the prothrombin time response to dicumarol.
6. The relation between the amount of dicumarol given and the typical response.
7. The effects of various conditions and characteristics of patients on the degree of response to dicumarol.
8. The prothrombin time levels characteristic of coronary thrombosis patients in the absence of anticoagulant therapy.

CHARACTERISTICS OF THE PROTHROMBIN TIME DATA

Methods and Techniques Used in Determining Prothrombin Time

The variations in techniques employed in determining the prothrombin time and the variety of thromboplastins utilized made it difficult to compare statistically the prothrombin times reported by the several hospitals participating in this study. To minimize this difficulty by standardization, detailed instructions as to procedures were circularized (see Appendix D). In addition, hospital laboratories were visited and laboratory supervisors and technicians invited to the Central Laboratory for special consultation or training. These efforts were not completely successful in securing conformity to standardized procedures, for the laboratory staffs of certain hospitals were unable or unwilling to readjust their methods and procedures for determining prothrombin time.

A review of the reported procedures and the findings on dilution curves for normal blood indicated that the prothrombin times reported by different hospitals were not uniformly comparable. Seven of the cooperating hospitals reported the method they used to be the Quick method and 9 hospitals reported that they used the Link-Shapiro modification of this method.* The thromboplastins used included several brands of commercial thromboplastin and thromboplastins produced by hospitals or special laboratories from a variety of biological sources, such as rabbit lung, rabbit brain, and human brain. They differed in some instances from those specified for the method reported. The diluents, the details of the laboratory techniques, and the methods of computing and reporting percentages also

* For descriptions of these procedures, see Appendix D and Marple and Wright,[111] pp 128-129, 336-338, 346-348

varied. Eight of the participating hospitals ran two determinations on each blood sample routinely and reported the average. The other eight hospitals ran only one test except when an error was suspected, exceptionally prolonged readings were obtained, or other special circumstances required a second reading. Some hospitals reported readings obtained with dilute plasma only and others, readings obtained with both undilute and dilute plasma. Some reported daily control figures; some applied single control figures for prolonged periods of time, and others, no control figures. Prothrombin times were determined daily or at longer intervals, particularly after the patient's response pattern had been observed during an initial trial period

Some of the consequences of these procedural differences are dramatically evident in Figure 144 which presents the medians for each hospital at five standard dilutions, 100, 50, 25, 12 5, 6.25 per cent. Each median is based on duplicate determinations for 10 normal blood samples tested under varying conditions. The actual figures, together with the corresponding means and ranges, are reported in Appendix F Table 74. For whole plasma, median findings varied from 12.5 to 18 seconds; at 12.5 per cent dilution, from 29 to 57 seconds; and at 6.25 per cent dilution, from 50 to 138 seconds. Some hospitals were consistently atypical at all dilution levels. [illegible]

times, and those produced by minute variations in laboratory techniques, varied one from another even more substantially, as an examination of the ranges will indicate. These results reflect the serious lack of standardization in the meaning of prothrombin times even among hospitals with high standards. *They also highlight the*

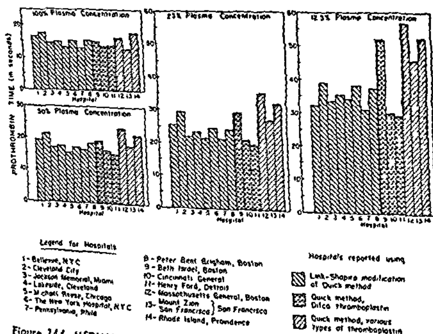


Figure 144. MEDIAN PROTHROMBIN TIMES FOR NORMAL PLASMA, BY HOSPITAL: Median prothrombin times (in seconds) found for ten normal blood samples at various plasma concentrations by participating hospitals using various methods and procedures for determining prothrombin time.

marked danger in interpreting reported prothrombin times without a knowledge of the corresponding normal blood findings for a given laboratory, preferably for the day in question. The experience in this study as well as elsewhere demonstrates, however, that satisfactory anticoagulant therapy can be carried out *in spite of this discrepancy, provided that the physician can interpret correctly the reports provided for him in the hospital in which he works.*

Standardization of Prothrombin Time Reports

Since the records from individual hospitals had to be consolidated to provide a sufficient number of observations for valid statistical analysis, some method of correcting for interhospital differences had to be devised.

Conversion Procedure

The procedure adopted provided, in essence, for the use, in all tabulations, of data corrected to apply to a standard dilution curve based on the medians for all hospitals using the Link-Shapiro modification of the Quick one-stage test. The major points in this curve are given as the second column of Table 139. A smooth curve drawn through these points is shown as the Link-Shapiro curve in Figure 145. A similar composite curve for hospitals reporting that they used *the Quick method crosses that for hospitals* using the Link-Shapiro modification, the whole plasma findings being less prolonged and those for the higher dilutions, more prolonged, than the Link-Shapiro times at corresponding dilutions. These curves represent, it must be remembered, not the times considered standard or ideal with these two *methods,* but rather the medians of actual times reported for blood tested by these methods by the cooperating hospitals under varying circumstances and with varying thromboplastins. Particularly at the low dilutions, the Quick medians are more prolonged than those specified for this method.[b] This divergence is understandable since rabbit-brain thromboplastins were not always used.

The conversion procedure adopted consisted essentially of correcting the readings reported for each patient for each day of therapy by the difference (measured in seconds at the percentage of prothrombin activity equivalent for that hospital to the

[b] See Marple and Wright,[m] page 338

TABLE 139

COMPOSITE PROTHROMBIN TIME DILUTION CURVES: Median Prothrombin Times at Each of Five Different Plasma Concentrations Computed from Reports on Ten Normal Blood Samples from Each of Six Cooperating Hospitals Reported Using the Quick Method and from Eight Reported Using the Link-Shapiro Modification[a]

Plasma Concentration (in Per Cent Whole Blood)	Median Prothrombin Time (in seconds)		
	All Hospitals Submitting Samples	Samples Tested by Hospitals Reported Using—	
		Link-Shapiro Modification of Quick Method (Comparable Thromboplastins) (8 Hospitals)	Quick Method (Various Types of Thromboplastin) (6 Hospitals)
100	15.0	15.2	14.6
50	18.6	18.2	19.0
25	24.8	23.7	28 1
12.5	37.2	35.5	47.1
6 25	62.5	59.8	97.6[c]

[a] Since San Francisco and Mt. Zion Hospitals used the same thromboplastin and the same methods and submitted their results jointly for this analysis, they are counted as one hospital in the above tabulation. They are represented by their findings with rabbit brain thromboplastin.

[b] Values differ from those reported by Quick because of differences in thromboplastins used and for other reasons. For values obtained by Quick, see Marple and Wright,[m] p. 338

[c] The 6.25 per cent dilution readings were estimated for one hospital by graphic interpolation since this hospital reported in terms of 10 per cent and 5 per cent instead of in terms of 6 25 per cent. Also, 6 samples from another hospital gave uncertain end points at the 6 25 per cent level and therefore had to be omitted in computing these medians.

number of seconds in question) between an appropriate median curve for a given hospital and the composite standardized curve adopted for the reporting of findings in this study. The necessary curves were fitted free-hand to the available medians but with all possible care, using double logarithmic paper and French curves to aid the process. For the most part the medians used were those reported in Appendix F, Table 74. For hospitals reporting an exceptional amount of scatter in day-to-day control times, daily variations in controls were also taken into account, special conversion tables being prepared for each control level.

As an additional precaution against a hidden consistent bias, the medians derived from the reported dilution curves (shown in Appendix F Table 74) were reported to the hospitals concerned and the staff was asked whether they represented typical findings for their laboratory for the period of the study. The whole plasma findings on these dilution curves were also checked for consistency with the daily control times recorded on the schedules and the hospitals questioned regarding major discrepancies. When the reported dilution curves clearly were not typical for a given hospital for all or part of the period of this study, the hospital concerned provided in each instance supplementary data from which other more typical curves could be developed for use in converting reported readings to the standardized curve.

The final conversion tables actually used

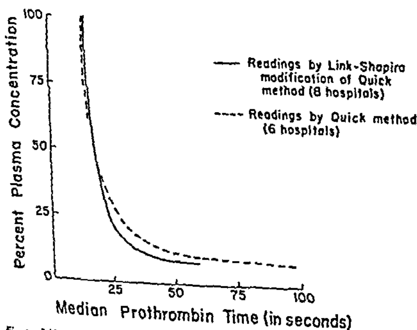


Figure 145. COMPOSITE PROTHROMBIN TIME DILUTION CURVES FOR NORMAL BLOOD. Composite prothrombin time dilution curve for normal blood based on medians for five different plasma concentrations, each median computed from reports on ten normal blood samples from each of eight hospitals reported using the Link-Shapiro modification of the Quick method and a corresponding curve based on similar data from six hospitals reported using the Quick method.

in the study are summarized in Appendix F, Table 75 (Parts I and II) which reports the seconds at each hospital considered equivalent to specified groups of seconds on the standardized curve, sometimes by control levels. Readings were rounded to the nearest whole second before conversion. Since the corrections involved in the conversion process represent the difference between medians for specific hospitals and those for the composite curve at corresponding dilutions, the corrections are, at best, approximate only. If for any reason, such as a laboratory error, a reported time was more or less prolonged than the true blood level would justify, this error would remain uncorrected after conversion. Most residual errors were probably counterbalancing and should not distort significantly the average picture as presented, although the occasional individual blood levels may be substantially distorted by the procedure adopted. (For example, if old thromboplastin was used on a given day by a hospital for which control times were either unreported or not used in conversion, the times both before and after conversion would be too high.)

Interpretation of Converted Seconds

The statistics resulting from these conversions are presented in tables throughout this chapter which report the findings by intervals stated in terms of both seconds and equivalent percentages of prothrombin activity on the composite curve. The reader may thus read each table in terms of either percentages or seconds as he wishes. He should be forewarned, however, that if he usually thinks in terms of seconds, the seconds in all tables probably have a different meaning from those to which he is accustomed. *Before using any findings from this chapter, the reader should convert the seconds as given in the tables to those he is most familiar with in his own hospital. This can be done by inquiring as to what seconds in his laboratory are equivalent to each of the percentages of prothrombin activity cited in these tables. If this conversion step is omitted, the findings with respect to the therapeutic range and other important phenomena may be misinterpreted and, in consequence, the results incorrectly applied clinically.*

For example, if a physician finds that 35 (instead of 25) seconds are equivalent to 23 per cent on the dilution curve for normal blood for his hospital, then 35 seconds as observed in his practice are the same as 25 seconds as used in this report. Failure to reinterpret readings in this manner might lead him to conclude that an observed time of 25 seconds in his laboratory was adequate when, in fact, it was equal to perhaps only 19 seconds as observed in this report. Conversely, divergencies of the opposite type might lead to an underevaluation of the hemorrhagic risk.

OPTIMUM THERAPEUTIC RANGE FOR PROTHROMBIN TIMES

With the aid of this conversion procedure for consolidating the experience of the individual hospitals, it was possible to determine the approximate prothrombin levels for undilute plasma at which both thromboembolic complications and hemorrhages were minimized. Unfortunately the evaluation of the therapeutic range for prothrombin times based on 12.5 per cent plasma was not feasible because not enough hospitals reported daily readings in terms of dilute plasma and because the difficulties of securing interhospital comparability by correction procedures increase greatly at the higher dilutions.

Method of Determining Therapeutic Range

The evaluation of the relative risks at different prothrombin levels for undilute plasma actually undertaken required not only counts of the complications and bleeding episodes occurring at each level, but also counts of the number of days patients had been maintained at these levels. To illus-

trate in extreme form the need for such dual counts, let it be imagined that seven bleeding episodes had been reported as beginning at times of 60 seconds or more. If there had been only 14 days on which patients reached these levels, the risk of bleeding would be computed as 50 per 100 days, or one every other day, whereas if the patients had been at such levels for 7000 days, the risk would be only 1 per 1000 days. In comparisons with other prothrombin time levels, the number of days of observation at a given level is obviously a factor of crucial importance.

To provide these necessary day counts for the evaluation of the optimum therapeutic range for prothrombin times, all undiluted plasma prothrombin times (over thirteen thousand) were converted to their approximate equivalent on the standardized curve and then tabulated by levels. In addition, all thromboembolic complications and hemorrhages (i.e., hemorrhages related to anticoagulants) were tabulated according to the prothrombin time on the day they were first observed The two sets of data were then related to secure rates. The analysis omitted (1) complications occurring on days when the patients were not under the influence of anticoagulants, (2) those occurring on days when the prothrombin times were not taken or not reported or could not be converted, and (3) those occurring under heparin. Patient-days in similar categories were also omitted. In view of the conversion procedure and the known variability in laboratory prothrombin times, the results are, of course, approximations only. It should not be implied from the relatively narrow and closely defined class intervals used to facilitate the location and definition of the therapeutic range that the individual readings tabulated were similarly exact.

Optimum Levels for Miminizing Thromboembolic Complications

The results are reported in Table 140 Appendix F, Table 76 presents similar data but excludes the days after the last dose. The same topic is also discussed briefly in the chapter on thromboembolic complications (Chapter VIII). They are shown graphically in Figure 146 (and also in Figure 95 of the chapter on thromboembolic complications). When the number of thromboembolic complications at each level is divided by the number of patient-days at this level, the resulting incidence rates form two clear plateaus. These rates remain at an almost constant level of about 5 per thousand days of observation for all prothrombin time intervals less than 25 seconds, regardless of the details by which rates are computed. Beginning at the 25 to 29 second interval, rates drop off abruptly to about half this figure, all rates of all types for levels of 25 seconds or more being between 2.2 and 3.2 per thousand days observed. *No further downward trend is apparent as times are prolonged beyond 25 seconds, times of 50 seconds and over having no better record for thromboembolic complications than times of 25 to 29 seconds.*

When the combined rate for all times less than 25 seconds (5 8 per 1000 days) was compared with that for all times of 25 seconds or more (2.6 per 1000 days),* it was found that the chances that this difference was a chance phenomenon were only about 2 per 100 (i.e., of "borderline significance" by definition adopted). The consistency of the pattern and its conformity to the expected consequences of anticoagulant therapy further substantiate the conclusion that the phenomenon is not a chance one.

It is reasonable to conclude, therefore, that *to receive full benefits of anticoagulant therapy, patients should be kept at all times at prothrombin levels of at least 25 seconds (25 per cent or less), but that prolongations substantially beyond this figure yield no clear*

* Rates here compared exclude the first day of dicumarol and days after the last dose (as quoted in Appendix F, Table 76), and to simplify the tests, are unweighted. When the rates are weighted, the difference remains 3 2 complications per 1000 d-

TABLE 140

THROMBOEMBOLIC COMPLICATION AND BLEEDING RATES AT VARIOUS PROTHROMBIN LEVELS DURING DICUMAROL THERAPY: Number of Thromboembolic Complications and Number of Bleeding Episodes Occurring at Various Prothrombin Levels from the Second Day of Dicumarol Therapy through Four Days after the Last Dose and Number per Thousand Days Patients Were Maintained at These Levels among All Patients in the Total Sample Receiving Dicumarol

Prothrombin Time (Converted)[a]		Number of Days Observed at Given Levels[a]	Number of Thromboembolic Complications Occurring at Given Prothrombin Levels[b]			Number of Bleeding Episodes Due to, or Aggravated by, Dicumarol Therapy and Beginning at Given Prothrombin Levels[b, d]		
			Total Number	Average Number per 1000 Days of Exposure to Risk at Given Prothrombin Levels		Total Number	Average Number per 1000 Days of Exposure to Risk at Given Prothrombin Levels	
In Seconds	In Per Cent Prothrombin Activity			As Reported	Weighted Average of Weekly Rates[c]		As Reported	Weighted Average of Weekly Rates[c]
Under 20	41% or over	2,234	10	4.5[e]	4.6[e]	4	1.8	2 2
20–22	40 –28.3	1,810	10	5.5	5 5	3	1.7	1 5
23–24	28.2 –23.7	1,204	6	5.0	5.4	5	4.2	5 1
25–29	23.6 –16 8	2,776	6	2.2	2.3	9	3.2	3 4
30–39	16.7 –10.9	3,162	9	2.8	2 8	12	3.8	3 8
40–49	10.8 – 7.84	1,092	3	2.7	2.6	8	7.3	7.5
50–59	7.83– 6.30	408	2	2.7	2.5	7	17.2	17.4
60 and over	6.29 and under	337				7	20.8	20 6
Total for all days of therapy with known readings		13,023	46	3.5	3.5	55	4.2	4 2
Total for days of unknown prothrombin times[f]. ..		3,214	12[g]	3.7	.	1[h]	...[h]	..[h]
Total for all days of dicumarol therapy		16,237	58	3.6	.	56	3.4	.

[a] To facilitate the location of the limits of the therapeutic range, narrower class intervals were used in some instances than would seem justified in view of the inaccuracies in the basic data. For method of conversion, see pp 350–352. Times cited refer to whole plasma.

[b] All counts include control group cases who received dicumarol as an exception and omit periods of heparin therapy. They exclude the first day of dicumarol therapy since dicumarol was influential at most for only a few hours of the first day and available prothrombin readings for this day apply uniformly to the hours prior to the beginning of anticoagulants. Counts also exclude days more than 4 days after the last dose since most cases had returned to normal by that time.

[c] Rates represent an approximation of what the rates for the various prothrombin levels would have been if the same prothrombin times had been maintained equally during all weeks of the illness. They were introduced to remove the spurious influence of the interrelations of the uneven distribution of prothrombin times by week of illness (see Appendix F Table 77) and the uneven distribution of complications by week of illness (see Table 98). See footnote c of Appendix F Table 76 for explanation of procedure employed.

[d] Bleeding episodes are classified according to the prothrombin level at the time the episode began (or was first believed influenced by dicumarol). In a few cases when no prothrombin time was reported for this day, the time interval was estimated where possible on the basis of the time on the preceding and following day and related facts

[e] Complication rates for prothrombin times under 20 were undoubtedly lowered by the use of heparin [illegible] from the present tabulation [illegible] hrombin readings could not be [illegible] times were reported and com-

additional advantage except that they increase the margin of safety by which drops below 25 seconds are avoided.

It is also clinically significant that the use of dicumarol even with little actual prolongation of prothrombin time seems to afford a measure of protection. During periods of the illness comparable to the period of anticoagulant therapy in the treated group, the control group experienced 12.6 complications per 1000 days, whereas those receiving anticoagulants, even during days when times were less than 25 seconds, experienced rates of less than half this amount (see Tables 140, 95 [Chapter VIII], and Appendix F, Table 76). The comparatively favorable record for patients under dicumarol but at prothrombin times below 25 seconds may be due in some measure to the omission of days under heparin, since heparin may have been used selectively in some instances to protect cases for whom the risk was believed exceptionally high. However, it is hardly conceivable that this is the major explana-

RATES FOR COMPLICATIONS AND BLEEDING
RELATED TO DICUMAROL, BY PROTHROMBIN LEVELS

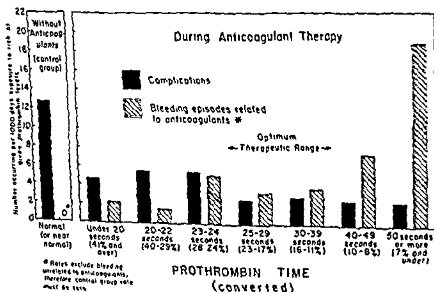


Figure 146. RATES FOR COMPLICATIONS AND BLEEDING RELATED TO DICUMAROL, BY PROTHROMBIN LEVELS: Number of thromboembolic complications and number of bleeding episodes related to dicumarol therapy per thousand days patients were maintained at various prothrombin levels from the second day of dicumarol therapy through four days after the last dose (weighted averages of weekly rates) for all patients in the total sample receiving dicumarol and corresponding rates for the control group for an *approximately* comparable period of the illness.

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plications for which the day of occurrence was unknown ... reported but could be estimated from the ... for the present tabulation. These cases ar ... known ... interval and not as un-

* When bleeding episodes began on days wh... was estimated ... me interval

tion for the low rate. Since relatively little heparin was used, it would seem more reasonable to conclude *that a little anticoagulant protection is definitely better than none. In cases where excessive hemorrhagic or other medical risk precludes the use of dicumarol in the usual doses, or maintenance of the usual prothrombin levels, consideration should be given to the use of minimal doses such as would maintain the patient at about 20 seconds prothrombin time.*

Optimum Levels for Minimizing Hemorrhagic Complications

The opposite type of relationship to prothrombin times is presented by the rates for bleeding episodes related to dicumarol, also shown in Table 140 and Figure 146. (See also Figure 124, Chapter IX, which presents the bleeding findings separately, and the related text.) Below 23 seconds, bleeding episodes related to anticoagulants were minimal (reported rates were less than 2 per 1000 days), but not entirely absent. Four such episodes occurred at times under 20 seconds and another 3, at times between 20 and 22 seconds inclusive. *Thus even minimal dicumarol therapy involves some risk of bleeding.*

Since these bleeding episodes are by definition "related to dicumarol" and are included because by medical evaluation they were considered probably due to, precipitated by, or aggravated by, dicumarol therapy, the corresponding rate for control cases, after corrections for exceptions in treatment, is zero. Bleeding unrelated to anticoagulants occurred, of course, in both the control and treated groups. These rates are discussed in detail in Chapter IX (on hemorrhages).

Beginning with 23 seconds, bleeding rates turned upward, the weighted average of weekly rates[d] for 23 to 24 seconds being 5.1 episodes per 1000 days of anticoagulant therapy with these times; that for 25 to 29 seconds, 3.4; and that for 30 to 39 seconds, 3.8. Probably within the range of 23 to 39 seconds the true bleeding risk varies little by prothrombin level, the observed variations, including the relatively high reading for 23 to 24 seconds, no doubt being due to chance fluctuations, the approximate nature of the prothrombin time conversions, errors in reporting, etc. A slight increase in bleeding risk must, however, be assumed to occur as times are prolonged from times below 23 seconds to times above this figure.

The more significant increase comes, however, at more prolonged times. Beginning with 40 seconds (10 per cent), the bleeding rate practically doubles. It more than doubles again between 50 and 59 seconds (7 per cent), and by the time 60 seconds (6 per cent) is reached, it is practically 5 times that for the range from 23 to 39 seconds, or 20.6 bleeding episodes per thousand days at times of 60 seconds or more.

When the intervals are combined into larger units, the bleeding rates[e] became:

Less than 25 seconds	2 3 per 1000 days
25-39 seconds	3 5 per 1000 days
40 seconds or more	12 0 per 1000 days

For the size of sample available, the difference between the rate below 25 seconds and that for 25 to 39 seconds is not statistically significant, but the difference between 25 to 39 seconds and 40 seconds or more is highly significant statistically.

Conclusion as to Therapeutic Range

The conclusion as to the approximate optimum therapeutic range for prothrombin times is obvious. All dicumarol therapy confers some protection against thromboembolic complications and involves some risk of bleeding. The increase in bleeding risk necessary to give the patient maximum instead of minimum protection against

[d] This type of rate was used to avoid distortion of the findings by the irrelevant association between the timing of the initial and terminal stages of therapy and the period of maximum and minimum risk of bleeding. The actual procedures involved are described in footnote c of Table 140.

[e] Rates apply to the period from the second day of dicumarol through four days after the last dose and are unweighted.

thromboembolic complications, namely, times of 25 seconds or more, is slight. Twenty-five seconds (i.e., 23 per cent) is therefore the obvious lower limit of the therapeutic range. *The upper limit is also obviously 40 seconds (i.e., about 11 per cent) since prolongation beyond this time increases rapidly the risk of bleeding without giving any observable increased protection against thromboembolic complications.*

These findings substantiate closely previous clinical impressions as to the desirable limits for prothrombin times, on the basis of which, at the outset of this study, times of at least 30 seconds but less than 50 seconds were recommended as a therapeutic guide. The present findings shorten these times slightly, but in general do not come as a surprise. This inductive statistical confirmation for clinical impressions serves to give a measure of reassurance to the procedures for anticoagulant therapy.

EFFECT OF CONSISTENCY IN CONTROL

Reported tabulations thus far have dealt only with prothrombin times *on the day complications or hemorrhages were first observed.* To determine whether consistency in the prothrombin times maintained was a factor in the onset of complications, thromboembolic complications were also tabulated according to whether the day on which the complication occurred *and the two preceding days* all showed prothrombin times of 30 seconds or more. (For example, a case in which an extension of the infarction occurred at 39 seconds and the two preceding days showed times of 34 and 35 seconds is

TABLE 141

THROMBO[illegible]

Type of Three-Day Prothrombin Time Sequence (Ending 4th Day of Dicumarol Therapy or Later)[b]	Number of Given Type of Sequences Reported *Ending during the* Period from the 4th Day of Dicumarol through the Day of the Last Dose[a] (Col. 1)	Number of Thromboembolic Complications: Total Number Reported to Have Developed on the Third Day of Sequences of Given Types during Therapy[a] (Col. 2)	Number of Thromboembolic Complications: Number per 1000 Three-Day Sequences of Given Types (Col. 2 ÷ Col. 1)
Three-day sequences ending in 30 seconds or more (i.e., 16.7% prothrombin activity or less)			
All three readings 30 seconds or more	2,149	4	1.9
All other sequences ending in 30 seconds	2,308	6	2.6
Three-day sequences in which the final reading was 25–29 seconds (i.e., 23.6% through 16.8% prothrombin activity)	2,479	6	2.4
Three-day sequences in which the final reading was under 25 seconds (i.e., 23.7% prothrombin activity or more)	3,855	16	4.2
All three-day sequences ending in a known prothrombin time[b]	10,791	32	3.0

[a] Counts include control cases receiving dicumarol [illegible] plication. Counts exclude complications pri[illegible] the fourth day, and [illegible]

[b] Cou[illegible] and 9 com[illegible] day of oc[illegible]

included here.) The results are given in Table 141 and Figure 147.

Only 4 thromboembolic complications in the entire study were found to have occurred when the prothrombin time for three successive days had been 30 seconds or more. Three of these were extensions of the original infarction and the fourth was a new infarction within the heart. None occurred outside the heart under such circumstances. The corresponding number of three-day sequences with all times 30 seconds or more that were known to have occurred among all patients studied was found to be 2,149. The complication rate for such sequences was thus 1.9 per 1000 corresponding three-day sequences, the lowest rate experienced by the patients in the present study under any of the circumstances analyzed.

The corresponding rate for all other three-day sequences ending in times of 30 seconds or more, that is, those with a mixed preceding sequence (as, for example, a sequence of 16, 25, and 31 seconds), was 2.6 per 1000 such sequences. An analysis into similar component rates was not undertaken for time sequences ending in 25 to 29 seconds since at the time such times were not recognized as therapeutically satisfactory. The rate for the total group of sequences ending in 25 to 29 seconds, without distinction as to preceding sequence, was 2.4 as contrasted with a rate of 4.2 for sequences ending in times of less than 25 seconds. *The advantage in respect to complications of a consistent record within the therapeutic range is obvious.*

The data confirm the observation made on a number of individual case records submitted that complications often developed at times when (1) prothrombin times had been allowed to drop below the therapeutic range, or (2) following such drops when times were again prolonged, or (3) during interruptions in dicumarol therapy.[t] *These undesirable fluctuations can be minimized by maintaining the patient on as consistent a daily dose as possible and by the use of divided daily doses. The use of high doses on*

[t] Figures illustrating such cases from the present series appear in Marple and Wright,[23] pp 174-179

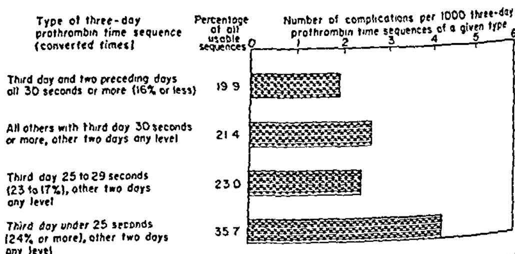


Figure 147. COMPLICATIONS IN RELATION TO PRECEDING PROTHROMBIN TIMES: *Number of thromboembolic complications occurring on the third day of various types of three-day prothrombin time sequences ending the fourth day or later of dicumarol therapy per thousand such three-day sequences observed among all patients receiving dicumarol.*

some days followed by several days entirely without dicumarol was observed to produce typically a spiked type of prothrombin curve with an unnecessarily high proportion of days both below and above the therapeutic range, with a concomitant increase in the hazard to the patient of either bleeding or a thromboembolic complication.

These findings provide some basis for an evaluation of the extent to which the present study achieved the minimum rate of thromboembolic complications possible in large unselected samples of hospitalized cases of coronary thrombosis with myocardial infarction, given a high level of accuracy in the clinical diagnosis of complications It is clear from Table 141 that *if all patients in the treated group not denied anticoagulants because of contraindications could have been maintained consistently at levels of 30 seconds or more from the fourth day of therapy through the day of the last dose, or in the case of unavoidable deviations, protected with heparin during deviations, the over-all record for thromboembolic complications from the fourth day on might well have been approximately a third more favorable.* This estimate is consistent with the very favorable rates some physicians have reported for other series (see Table 93, Chapter VIII) There is danger, however, in assuming that differences between series are necessarily the result of more effective control since such differences may also reflect differences in the type of population covered, differences in the proportion of complications diagnosed clinically, and chance differences

RATES IN "RELATIVELY IDEAL" VERSUS "NONIDEAL" THERAPY

That consistent control of prothrombin times does improve the outlook for the patient is emphasized once again by still another statistical approach to the basic data. Table 142 and Figure 148 divide the treated cases surviving to the sixteenth day after the attack into those receiving "relatively ideal" therapy from the point of view of prothrombin times and length of anticoagulant therapy, those receiving therapy that was "clearly not ideal," and those for whom the adequacy of therapy could not be classified. After a review of the records, it was decided that cases surviving less than 16 days should be excluded from the comparisons since the delays involved in hospitalization, diagnosis, and the initial rise in prothrombin times rendered the period of dicumarol therapy in such cases usually too short for evaluation. For purposes of this analysis "relatively ideal therapy" was defined on the basis of recommended procedures as therapy in which:

1. Anticoagulants were begun not later than the 7th day of the illness.
2. Anticoagulants were continued for at least 21 days (or until death).
3. Prothrombin times were maintained between 25 and 49 seconds (converted times) from the 4th day of anticoagulants through the day of the last dose, with the exception of no more than 3 readings below 25 seconds and no more than 3 readings above 49 seconds

The details of the definition selected are arbitrary, but precise dividing lines were necessary for the statistical treatment of the records. The criteria do not seem particularly high since an earlier beginning, a longer continuation, a narrower therapeutic range, and fewer exceptions are actually recommended and clearly desirable. Nevertheless, even with this leniency, only 70 cases, or 14 per cent of the 509 cases covered by the tabulation, met these requirements. If no exceptions had been allowed under requirement 3 above, only 8 cases in the entire study would have qualified. Consequently, a stricter definition of "relatively ideal therapy" was not practical statistically Probably a stricter definition would have also been unrealistic medically, for *perfect control is exceedingly difficult to achieve, as is strikingly demonstrated by the fact that only 1.6 per cent of the treated group*

were maintained without exception between 25 and 49 seconds.

Since 70 cases receiving "relatively ideal therapy" are admittedly a small number from which to judge, and since the group is somewhat selected, due to the omission of early deaths, their record on thromboembolism and bleeding must be considered *suggestive only. Their experience does,* however, confirm the value of close prothrombin time control and maximum coverage of the period of danger. Among these 70 cases, the number of thromboembolic complications developing during anticoagulant therapy was only 4.3 per hundred cases as compared with 8.0 per hundred among the 423 cases clearly not receiving ideal therapy. *Since the 70 probably re-*

TABLE 142

"RELATIVELY IDEAL" AND "NONIDEAL" ANTICOAGULANT THERAPY *IN RELATION TO* THROMBOEMBOLIC COMPLICATION AND BLEEDING RATES: Number of Thromboembolic Complications and Number of Bleeding Episodes Related To Anticoagulant Therapy, and Number of Each per Hundred Cases *Occurring during Anticoagulant Therapy among Cases in the* Treated Group Who Survived to the Sixteenth Day after the Attack and Did, or Did Not Receive Dicumarol Therapy Conforming to Relatively Ideal Standards

Standard of Anticoagulant Therapy Maintained	Treated Group Cases Receiving Dicumarol and Surviving through 15th Day				
	Number of Cases[a]	Thromboembolic Complications (4th Day of Anticoagulants through End of Such Therapy[b])[c]		All Bleeding Episodes Related to Anticoagulant Therapy[c]	
		Total Number	Number per 100 Cases	Total Number	Number per 100 Cases
"Relatively ideal therapy"[d]	70	3	4.3	10	14.3
"Therapy clearly not ideal"[e]	423	34	8.0	41	10.0
Therapy the adequacy of which was indeterminate[f]	16	—	*0.0*	—	*0.0*
Total cases in the treated group receiving dicumarol and surviving through the 15th day[a, g] ..	509	37	7.3	51	10.0

Note: *Italics are used when rates quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Cases dying before the 16th day were omitted because such cases were not followed long enough to justify a judgment as to the adequacy of their therapy.

[b] *Defined to include the first 4 days after the last dose. Periods of heparin* therapy are included in computing dates.

[c] Complications and hemorrhage counts include the first 15 days but are limited to periods of therapy within the first six weeks following the attack. Hemorrhage counts include bleeding episodes probably due to, or aggravated by, anticoagulant therapy.

[d] Defined as anticoagulant therapy begun not later than the 7th day of the illness and continued at least 21 days, or until death, with doses that maintained the prothrombin time between 25 and 49 seconds *(converted time) from the 4th day of anticoagulants* through the day of the last dose, with the exception of no more than 3 readings below 25 seconds and no more than 3 above 49 seconds.

[e] Defined as all therapy clearly not meeting the standard as defined in footnote d. This category includes cases for which anticoagulant therapy was not begun until after the seventh day, cases not maintained on anticoagulant therapy for at least 21 days or (in cases of death) until the day of death, and cases not maintained within the range of prothrombin time specified for "relatively ideal therapy," or having more than the allowable number of exceptions.

[f] *Cases whose prothrombin times could not be converted are included here.*

[g] Tabulation excludes all cases not receiving anticoagulants for any reason and cases receiving heparin only, but includes those receiving both heparin and dicumarol.

ceived anticoagulants on the average for longer periods than the 423, figures which took account of this factor might show an even greater difference in favor of adequate and sustained control. The 8 cases with no readings in the period that were less than 25 seconds or greater than 49 seconds developed no thromboembolic complications and no bleeding episodes. Unfortunately, 8 cases is too small a number for generalization. The findings for the 70 cases receiving "relatively ideal therapy," however, support further the previous estimate that with adequate prothrombin time control, the thromboembolic rate for the treated group in this study after the fourth day of anticoagulants could have been reduced at least a third below the reported rate.

For bleeding episodes related to anticoagulants, the rate for the "relatively ideal therapy" group shown in Table 142 is slightly less favorable in comparison with the "clearly not ideal therapy" group than that for complications, the relative rates being in this case 14.3 and 10.0 per 100 cases. The somewhat higher rate for the "relatively ideal therapy" group probably reflects both the exceptions allowed with respect to high prothrombin times and the unavoidable risk of bleeding inherent in good therapeutic protection against thromboembolic complications.

In general, it may be concluded from this

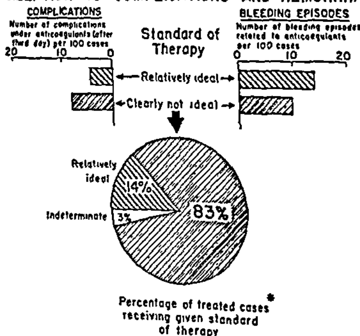


Figure 148. STANDARDS OF ANTICOAGULANT THERAPY IN RELATION TO COMPLICATIONS AND HEMORRHAGES: Average number of thromboembolic complications during anticoagulant therapy (after the third day) and average number of hemorrhages related to anticoagulants per hundred cases among cases in the treated group who survived at least to the 16th day after the attack and did or did not receive dicumarol therapy conforming to relatively ideal standards and percentage of such cases receiving given standard of therapy.

were maintained without exception between 25 and 49 seconds.

Since 70 cases receiving "relatively ideal therapy" are admittedly a small number from which to judge, and since the group is somewhat selected, due to the omission of early deaths, their record on thromboembolism and bleeding must be considered suggestive only. Their experience does, however, confirm the value of close prothrombin time control and maximum coverage of the period of danger. Among these 70 cases, the number of thromboembolic complications developing during anticoagulant therapy was only 4.3 per hundred cases as compared with 8.0 per hundred among the 423 cases clearly not receiving ideal therapy. Since the 70 probably re-

TABLE 142

"RELATIVELY IDEAL" AND "NONIDEAL" ANTICOAGULANT THERAPY IN RELATION TO THROMBOEMBOLIC COMPLICATION AND BLEEDING RATES: Number of Thromboembolic Complications and Number of Bleeding Episodes Related To Anticoagulant Therapy, and Number of Each per Hundred Cases Occurring during Anticoagulant Therapy among Cases in the Treated Group Who Survived to the Sixteenth Day after the Attack and Did, or Did Not Receive Dicumarol Therapy Conforming to Relatively Ideal Standards

Standard of Anticoagulant Therapy Maintained	Treated Group Cases Receiving Dicumarol and Surviving through 15th Day: *Number of Cases*[a]	Thromboembolic Complications (4th Day of Anticoagulants through End of Such Therapy[b])[c]: Total Number	Thromboembolic Complications: Number per 100 Cases	All Bleeding Episodes Related to Anticoagulant Therapy[c]: Total Number	All Bleeding Episodes: Number per 100 Cases
"Relatively ideal therapy"[d]	*70*	*3*	4.3	10	14.3
"Therapy clearly not ideal"[e]	423	34	8.0	41	10.0
Therapy the adequacy of which was indeterminate[f]	16	—	*0.0*	—	0.0
Total cases in the treated group receiving dicumarol and surviving through the 15th day[a, g]	500	37	7.3	51	10.0

Note: *Italics are used when rates quoted have less than 30 cases as a base since chance factors render such rates particularly unstable.*

[a] Cases dying before the 16th day were omitted because such cases were not followed long enough to justify a judgment as to the adequacy of their therapy.

[b] Defined to include the first 4 days after the last dose. Periods of heparin therapy are included in computing dates.

[c] Complications and hemorrhage counts include the first 15 days but are limited to periods of therapy within the first six weeks following the attack. Hemorrhage counts include bleeding episodes probably [illegible]

[illegible] of the illness and continued at [illegible] bin time between 25 and 49 seconds (converted time) from the 4th day of anticoagulants through the day of the last dose, with the exception of no more than 3 readings below 25 seconds and no more than 3 above 49 seconds.

[e] Defined as all therapy clearly not meeting the standard as defined in footnote d. This category includes cases for which anticoagulant therapy was not begun until after the seventh day, cases not maintained on anticoagulant therapy for at least 21 days or (in cases of death) until the day of death, and cases not maintained within the range of prothrombin time specified for "relatively ideal therapy," or having more than the allowable number of exceptions.

[f] Cases whose prothrombin times could not be converted are included here.

[g] Tabulation excludes all cases not receiving anticoagulants for any reason and cases receiving heparin only, but includes those receiving both heparin and dicumarol.

hospital medians showed a similar variability. The general mean for all hospitals included in this tabulation and for all usable readings during the period was 30 seconds and the median, 28. In other words, half of the readings after the third day were less than 28 seconds. The inadequacy of the levels prevailing is again apparent

Since the maximum effect of a given dose of dicumarol is not reflected in the prothrombin time for periods of 72 hours or longer, the actual record for all hospitals can be judged more fairly with data that eliminate the initial and terminal periods of therapy. This is accomplished in Figure 150, which portrays the distribution of prothrombin times at each stage of therapy. Supporting data appear in Appendix F, Table 79. During the period from the fourth day of dicumarol therapy through the day of the last dose, 36 per cent of the usable readings were below 25 seconds (i.e., 24 per cent or more of prothrombin activity) and 59 per cent were less than 30 seconds (above 17 per cent). *Control of patients in regard to excessive prolongation was more adequate*, only 6 per cent of the readings being prolonged to 50 seconds or more (7 per cent or less). Lack of experience in prescribing those doses which are required to bring patients' prothrombin times quickly to the desired levels, differences of judgment as to the levels desirable, and fear of hemorrhage appear to have been the major deterrents to adequate administration of dicumarol. As the project progressed and experience was gained, more adequate levels were maintained.

Delay in Response to Dicumarol

Figure 150 also brings into sharp focus a major problem in dicumarol therapy,

PROTHROMBIN LEVELS BY WEEK OF ILLNESS

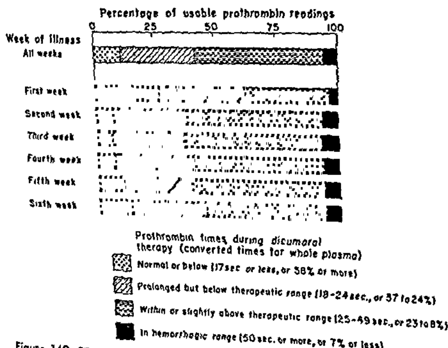


Figure 149. PROTHROMBIN LEVELS BY WEEK OF ILLNESS: Percentage of usable prothrombin readings during *dicumarol* therapy falling at various levels, by week of illness.

tabulation, as from the preceding, that *consistent maintenance of the patient within the proposed therapeutic range will reduce the risk of thromboembolism without a serious or excessive increase in the risk of bleeding.* The data do not support the inference that adequate control of prothrombin times will eliminate either thromboembolic complications or bleeding completely.

PROTHROMBIN TIME LEVELS MAINTAINED DURING ANTICOAGULANT THERAPY

General Levels

A review of the actual prothrombin time data on a patient-day basis will serve to indicate more precisely the actual levels maintained in practice during this study and the extent to which they conformed to optimum standards. At the outset of the study no statistical data were available with which to determine optimum prothrombin levels for dicumarol therapy. On the basis of clinical experience, the original instructions to the hospitals recommended that patients be kept at prothrombin times between 30 and 50 seconds, if times were tested by the Link-Shapiro modification of the Quick one-stage method. Recommended dosage schedules (see Chapter II) were designed to achieve these levels. It was understood that these recommendations were advisory only and that those actually produced were the responsibility of the physician in charge in each case.

The actual record for the present study is portrayed in Figure 149. Supporting data appear in Appendix F, Table 77. Of 13,416 patient-days of dicumarol therapy with usable prothrombin readings (including the first day of dicumarol), 52 per cent had times between 25 and 49 seconds and 44 per cent, *times between 25 and 39 seconds, the range later defined as the optimal range.* Only 32 per cent fell within the range of 30 to 50 seconds originally recommended for the cases included. The great majority of the deviant readings were *shorter* than the recommended range, 42 per cent of all readings being less than 25 seconds and 19 per cent, less than 20 seconds. Only 5.5 per cent were at the level of 50 seconds or more where the risk of bleeding is particularly high.

Figure 149 and Appendix F, Table 77 also present the prothrombin time distribution by week of illness. The problem of short times is most acute in the first week of the illness when patients' times must be prolonged for the first time and the incidence of thromboembolic complications is high. During this first week only 58 per cent of the total patient-days were spent under anticoagulant therapy (see Appendix F, Table 36) and of days in this week that were spent under dicumarol with known times, only 38 per cent had times of 25 seconds or more. By the second week, 62 per cent of the known times under therapy were prolonged to 25 seconds or more. On the whole the maximum prolongation was achieved in the third week of the illness. Thereafter times declined gradually as dicumarol therapy was terminated for some patients. In general, one must conclude from Figure 149 that protection during the first four weeks after the attack when the incidence of complications is especially high was considerably less than optimum.

That policies in regard to the prothrombin levels maintained tended to vary substantially from hospital to hospital is demonstrated by an inspection of Appendix F, Table 78, which gives means, medians, and distributions for all participating hospitals whose times could be converted. Four participating hospitals maintained times for their treated group patients from the fourth day of dicumarol therapy through the last dose that averaged below 25 seconds on the standardized curve, while another 4 hospitals maintained times that averaged between 25 and 29 seconds. Three hospitals, on the other hand, maintained times averaging in the upper 30's or more, the longest mean for any hospital being 41 seconds

small and indeterminate and because the anticoagulant properties of heparin greatly exceed any influence thus reflected. The success of heparin in protecting patients from thromboembolic complications in this early period is reported in Chapter X.

Prolonged Effect of Dicumarol

The protracted response of the prothrombin time to dicumarol is evident upon the termination of therapy. Since dicumarol therapy is not terminated ordinarily until the risk of thromboembolic complications is again minimal, the long-continued action of dicumarol becomes important at this point only when hemorrhage is present or threatened, or surgery is contemplated. Awareness of this problem may, however, be a deterring factor to the physician in planning the dosage level throughout therapy.

In the present study, the hospitals usually discontinued the determination of the prothrombin time on the day of the last dose of dicumarol or the day after. Only 190 patients were followed for at least 4 days after the last dose. The records of these patients

TABLE 143

TIME REQUIRED FOR [illegible]
DOSE OF DICUM[illegible]
bers of Days after t[illegible]
bin Times and Dic[illegible] at Beginning of Downswing

Dosage of Dicumarol (in mg.) and Prothrombin Time (Converted)[a] at Time of Termination of Therapy	Mean Days to Normal	Range of Days to Normal	Total Cases with Days to Normal Known	Number of Cases[b] First Reaching Normal Prothrombin Times[c] Given Numbers of Days after the Last Dose				
				1-2 Days	3-4 Days	5-6 Days	7-8 Days	9 or More Days
Total dose of dicumarol on last two days of therapy:								
Less than 200[d]	3.8	1-12	65	21	22	16	4	2
200-299	*4.1*	*1-8*	28	5	11	8	4	—
300 or more	*5.5*	*1-15*	13	4	3	3	—	3
All cases with adequate downswing records[b]	4.1	1-13	106	30	36	27	8	5
Prothrombin time on day of last dose:								
Under 20	*2.1*	*1-5*	28	20	7	1	—	—
20-29	4.3	1-13	55	9	23	19	2	2
30-39	*5.9*	*2-12*	21	1	6	6	5	3
40 or more	—[e]	—[e]	2	—	—	1	1	—
All cases with adequate downswing records[b]	4.1	1-13	106	30	36	27	8	5

Note: *Italics are used when means and ranges quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] For equivalents in terms of per cent prothrombin activity and method of conversion, see Table 140 and pp. 350-352.

[b] Tabulation includes only cases 1) who received dicumarol, 2) whose records reported prothrombin determinations after the last dose until the patient's time reached 17 seconds or less, 3) whose prothrombin time on the day of the last dose was known, and, 4) whose dicumarol dosage on the last two days was known. Control cases receiving dicumarol as an exception are included.

[c] Defined as 17 seconds or less (in converted seconds).

[d] All except 6 cases in this category received 100-190 mg.

[e] Not computed since there were fewer than 10 cases in the group.

namely, the delay in response to given doses of the drug. This is well illustrated in the record for the first three days of anticoagulant therapy. The findings for the first day indicate the prothrombin levels existing prior to the institution of therapy since these readings were uniformly taken before the first dose of dicumarol was administered. The occasional high readings represent cases with hypoprothrombinemia resulting from physiological causes such as liver damage. By the time the prothrombin times were determined on the second day, usually slightly less than 24 hours after the initial dose of dicumarol, only 12 per cent of the patients had prothrombin times prolonged *to 25 seconds (the minimum of the therapeutic range as later established) and only* 19 per cent were times prolonged to 23 seconds. By the morning of the third day *(i.e., within somewhat less than 48 hours on* the average), only 41 per cent had times prolonged to 25 seconds. When all usable readings taken within the first three days were considered together, 80 per cent were found to be less than the therapeutic minimum of 25 seconds. *These findings suggest the need for supplementation with quicker-acting anticoagulants such as heparin or Tromexan during this initial period if the patient is to be protected adequately against thrombo-embolic complications.*

These data describe patients receiving dicumarol only. At the time of this study the only other available anticoagulant was heparin. *Heparin was used on a total of 179* patient-days during the first three days of anticoagulants, or a total of 10 per cent of *all patient-days in this* initial period. These days under heparin are not included in the tabulations in this chapter because the influence of heparin on prothrombin times is

PROTHROMBIN LEVELS DURING VARIOUS STAGES OF DICUMAROL THERAPY

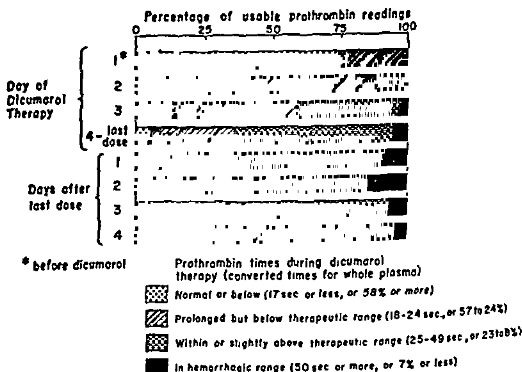


Figure 150. PROTHROMBIN LEVELS DURING VARIOUS STAGES OF DICUMAROL THERAPY: Percentage of usable prothrombin times during dicumarol therapy falling at various levels during various stages of dicumarol therapy.

ians customarily regulated subsequent loses according to the initial response of the patient, thus further obscuring the picture. For example, among those receiving 300 mg. on the first day and 200 mg. on the second day, 85 per cent of those who received no anticoagulant on the third day reached 25 seconds by the 4th day as contrasted with only 45 per cent of those who received 200 mg on the 3rd day. Thus those who received the lower dose gave the quicker response. The explanation lies in the fact that those who were responding rapidly were for this reason given less dicumarol on the 3rd day and those who were responding slowly were given more, thus rendering the dosage groups unequal biologically in their inherent speed of response A corresponding tabulation, not reproduced, showing the percentages reaching 30 seconds in relation to specific initial dosage sequences was similarly inconclusive.

All that can be deduced is that *relatively few of the participating physicians gave doses the first three days sufficiently high to achieve optimal therapeutic levels by the 4th or 5th day of dicumarol therapy.* Of the 455 cases whose days to 25 seconds were known, only 59 per cent reached 25 seconds by the 4th day, 71 per cent by the 5th day, and 81 per cent, by the 6th day. For 442 cases whose days to 30 seconds were known, only 37 per cent reached 30 seconds by the 4th day, 50 per cent by the 5th day, and 61 per cent, by the 6th day. Of cases treated at least 14 days and considered usable in these tabulations,

TABLE 144

DOSAGE IN INITIAL PERIOD IN RELATION TO TIME REQUIRED TO REACH 25 SECONDS: Cumulative Percentage of Cases Receiving Dicumarol and Having Usable Prothrombin Records First Reaching Prothrombin Times of 25 Seconds or Longer on or before Specific Days of Dicumarol Therapy, by Total Dosage of Dicumarol Received during the First Three Days of Dicumarol Therapy

Day of Dicumarol Therapy	Cumulative Percentage[a] of Cases Reaching Prothrombin Time of 25 Seconds or More (23 6 Per Cent or Less) on or before Given Day of Dicumarol Therapy							
	All Usable[b] Cases	Cases Receiving Total Dosage of Dicumarol (in mg) during First Three Days of Dicumarol Therapy of—						
		100-299	300-399	400-499	500-599	600-699	700-799	800-999
1st	1	—	2	—	2	2	—	2
2nd	9	*10*	11	10	7	6	9	12
3rd	36	*40*	35	27	38	39	37	41
4th	59	*60*	49	48	65	64	51	76
5th	71	*60*	60	56	75	80	70	93
6th	81	*70*	73	71	81	90	81	95
7th	86	*80*	75	76	86	94	88	95
8th	88	*80*	78	80	88	97	91	95
9th or 10th	90	*80*	78	85	88	98	93	98
11th or 12th	92	*90*	89	86	89	98	95	98
13th or 14th[c]	93	*90*	93	86	89	98	98	98
	Number of Cases with Usable[b] Records							
All cases receiving dicumarol	455	10	55	88	111	106	43	42

Note: Italics are used when percentages quoted have less than 30 cases as a base since chance factors render such rates particularly unstable

[a] Based on total number of cases with usable records in dosage subgroup.

[b] For definition of usable record, see footnote a of Appendix F Table 80.

[c] Of the 455 cases with usable records, 23 were treated over two weeks and never reached 25 seconds and 10 others reached 25 seconds only after the 14th day.

were used as the basis for estimates for all cases, the results of which are presented in Figure 150 and Appendix F, Table 79. The return to normal times is obviously slow. By the fourth day (i.e., 96 hours after the last dose), only 44 per cent of the patients had returned to relatively normal times. (Normal was defined as 17 seconds or less on the standardized curve, or 58 per cent or more, since only a small percentage, namely, 8 per cent, of readings for normal blood were above this level—see Appendix F, Table 84.) Five per cent of the patients still had times of 50 seconds or more. Doubtless there is some selection in the cases included among the 190, those in which high times were a problem being more frequently selected for continuing observation than those obviously past any danger of bleeding. Nevertheless, the slow response to dicumarol is obviously reflected in these terminal records, though for the average case the return to normal times may be slightly faster than that indicated.

For 106 of the cases, prothrombin readings were continued until the patients again reached normal times of 17 seconds or less. An analysis of these records is given in Table 143. The prothrombin times of these patients did not become normal for about 4 days on the average, but individuals varied greatly in this respect. Thirty reached normal within 1 or 2 days and 5 required 9 or more days, the maximum being 13 days. The two variables made obvious in the analysis are the amount of the dose on the last two days of therapy and the prothrombin time on the day of the last dose, both of which have the expected effect on the speed of return to normal, as the trends in the means clearly indicate. Both of these factors must be considered in estimating when the prothrombin time of the patient will be back to normal. The occasional delay is also important medically since prothrombin times cannot be assumed to be normal until they have actually been demonstrated to be normal. Subsequent experience as reported by Wright[257, 258] has shown that with Tromexan and phenylindanedione both the delay in response and the delay in return to normal are reduced. A subsequent study of Tromexan that deals with this point is reproduced as Appendix A of this report.

PROTHROMBIN LEVELS IN RELATION TO DOSAGE

A description of the amounts of dicumarol received by these patients will serve to indicate what doses on the average will achieve and maintain prothrombin times at the levels desired. Such data also re-emphasize the well-recognized variability in individual response.

Relation of Dosage to Delay in Obtaining Effective Blood Levels

The initial doses that were customary and the typical responses are indicated in Appendix F, Table 80. The most popular sequence (used for 53 patients) was 300 mg. the first day, 200 the second, and 100 the third. When this sequence was used, the prothrombin time reached 25 seconds by the 4th day in 64 per cent of the patients involved, in 83 per cent by the 5th day, and in 92 per cent by the 6th day or earlier. All other sequences used for 10 or more patients for whom the time 25 seconds was reached was known are listed in Appendix F, Table 80 The variety in dosage was extreme after the first day but most patients were started on 300 mg the first day. Occasionally 200, 100 or 400 mg. was used as the initial dose. The highest total dose given for the first 3 days was 900 mg., or 300 mg. on each of the first 3 days.

This tabulation was originally designed to demonstrate which dosage sequence is most effective on the average in securing a rapid rise into the therapeutic range. In this respect, it was not successful. The great variety of dosage combinations reduced the number of usable cases for each combination to the point where most rates were unstable for chance reasons alone. In addition, phys

ived between 600 and 900 mg. during this eriod, but again the variations between dividuals were marked. Two cases received s high as 1800 and 1899 mg. in this period hile 11 others received less than 400 mg. gain, as will be observed in Table 146, otal doses show some slight relation to the verage increase in prothrombin times chieved, indicating that adjustments of ter doses to the patient's initial reaction id not fully counteract the initial response.

Figure 152 shows the proportion of patients in each dosage group during the first eek whose prothrombin time from the third hrough the ninth day was prolonged on the verage less than 8 seconds, 8 to 15 seconds, nd 16 seconds or more as computed from he standardized curve. Since averages and ot minimum readings are involved, only he last of these classes could be considered dequate protection, the second being borderline and the first clearly inadequate. On

TABLE 145

TOTAL DICUMAROL DOSAGE USED IN FIRST WEEK. Number and Percentage of Cases Receiving Various Amounts of Dicumarol during the First Week of Dicumarol Therapy

Total Dose of Dicumarol in First Week (in mg.)	Cases with Usable Records Receiving Dicumarol Nine Days or More[a]	
	Number of Cases	Percentage of Total Cases
Less than 400	11	3
400–499	27	6
500–599	42	10
600–699	66	15
700–799	71	16
800–899	71	16
900–999	56	13
1,000–1,099	45	10
1,100–1,199	18	4
1,200–1,299	18	4
1,300–1,399	6	1
1,400 and over	9	2
Total usable cases	440	100

[a] Counts were secured when preparing Table 146 and include only cases suitable for this tabulation. For specifications, see footnote c, Table 146.

TABLE 146

AVERAGE PROLONGATION OF PROTHROMBIN TIMES DURING FIRST NINE DAYS: Number and Percentage of Cases Showing Various Average Numbers of Seconds of Prolongation of Prothrombin Times from the Third through the Ninth Day of Dicumarol [illegible]

Average Number of Seconds Prolongation of Whole Plasma Prothrombin Time[a] (Converted)[b] 3rd through 9th Day of Dicumarol	Cases with Usable Records[c] Receiving Dicumarol Nine Days or More		
	Number of Cases	Percentage of Cases	Average Total Dose of Dicumarol during First Week of Dicumarol (in mg.)
0 – 3.9	36	8	753
4.0– 7.9	113	26	812
8.0–11.9	100	23	827
12.0–15.9	75	17	875
16.0–19.9	57	13	808
20.0–23.9	35	8	830
24.0–27.9	16	4	*850*
28.0–31.9	6	1	—[d]
32.0–35.9	2	—[e]	—[d]
Total usable cases[c]	440	100	823

Note. *Italics are used when averages quoted have less than 50 cases as a base since chance factors render such means particularly unstable.*

[a] Represents the arithmetic mean of the number of seconds by which the daily readings from the 3rd to the 9th day exceeded the last prothrombin reading immediately before dicumarol was begun. Readings below 15 seconds were counted as 15. For shortcomings of the mean as a measure for prothrombin time increases, see footnote a, Appendix F Table 83.

[b] For method of conversion, see pp. 350-352.

[c] No increase was computed for 169 cases for one or more of the following reasons: 1) less than 4 readings, including the 1st day reading, were available for period; 2) heparin was received [illegible]

68 never reached 30 seconds and 23 never reached even 25 seconds. *The price of this delay in prolongation is reflected in the data on thromboembolic complications occurring during anticoagulant therapy as given in Chapter VIII.*

Table 144, Appendix F Table 81, and Figure 151 analyze the initial rise in relation to dosage from a slightly different angle, namely, in relation to *total dosage* during the first three days. The relation of the higher doses to a more rapid climb to seconds within the optimal therapeutic range is here somewhat more evident in spite of the tendency of physicians to increase the dose when the initial response was low. Sixty per cent or less of each subgroup of patients receiving total doses in the first three days of less than 500 mg. reached 25 seconds by the 5th day, whereas 93 per cent of those who received 800 to 900 mg. in the period reached 25 seconds by the 5th day. The general relation of delayed response to low total dosage is also roughly apparent in Figure 151. The lack of adequate doses is indicated by the fact that by the 8th day, 12 per cent of the patients had not yet reached 25 seconds. Initial doses larger than those actually given were clearly needed in most cases for speedy and optimal protection.

Of the variety of initial doses received, those totalling 400 to 700 mg. in the first three days were most typical. The range of individual variations was wide. More than 40 patients received 800 to 900 mg. in this period, while 65 received less than 400 mg. These variations reflect both differences in policy and differences in the patients' response patterns.

Table 145 and Appendix F, Table 82 extend the dosage period studied to include the entire first week. When 7 instead of 3 days are included, the average total dose becomes 823 mg. About half the patients re-

INITIAL DOSAGE IN RELATION TO TIME REQUIRED TO REACH PROTHROMBIN TIME OF 25 SECONDS

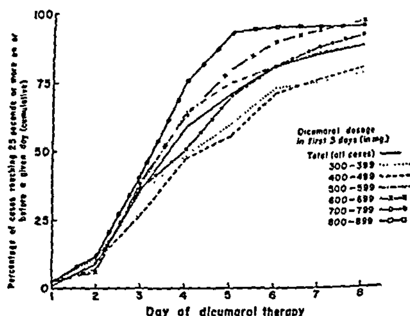


Figure 151. INITIAL DOSAGE IN RELATION TO TIME REQUIRED TO REACH PROTHROMBIN TIME OF 25 SECONDS: *Cumulative percentage of cases receiving dicumarol and having usable records who reached prothrombin times of at least 25 seconds (23 per cent or less) on or before specific days of dicumarol therapy, by dosage received during first three days.*

[rece]ived between 600 and 900 mg. during this [p]eriod, but again the variations between [in]dividuals were marked. Two cases received [a]s high as 1800 and 1899 mg. in this period [w]hile 11 others received less than 400 mg. [A]gain, as will be observed in Table 146, [t]otal doses show some slight relation to the [a]verage increase in prothrombin times [a]chieved, indicating that adjustments of [l]ater doses to the patient's initial reaction [d]id not fully counteract the initial response.

Figure 152 shows the proportion of pa[t]ients in each dosage group during the first [w]eek whose prothrombin time from the third [t]hrough the ninth day was prolonged on the [a]verage less than 8 seconds, 8 to 15 seconds, [a]nd 16 seconds or more as computed from the standardized curve Since averages and not minimum readings are involved, only the last of these classes could be considered adequate protection, the second being borderline and the first clearly inadequate. On

TABLE 145

TOTAL DICUMAROL DOSAGE USED IN FIRST WEEK: Number and Percentage of Cases Receiving Various Amounts of Dicumarol during the First Week of Dicumarol Therapy

Total Dose of Dicumarol in First Week (in mg.)	Cases with Usable Records Receiving Dicumarol Nine Days or More[a]	
	Number of Cases	Percentage of Total Cases
Less than 400	11	3
400–499	27	6
500–599	42	10
600–699	66	15
700–799	71	16
800–899	71	16
900–999	56	13
1,000–1,099	45	10
1,100–1,199	18	4
1,200–1,299	18	4
1,300–1,399	6	1
1,400 and over	9	2
Total usable cases	440	100

[a] Counts were secured when preparing Table 146 and include only cases suitable for this tabulation For specifications, see footnote c, Table 146.

TABLE 146

AVERAGE PROLONGATION OF PROTHROMBIN TIMES DURING FIRST NINE DAYS: Number and Percentage of Cases Showing Various Average Numbers of Seconds of Prolongation of Prothrombin Times from the Third through the Ninth Day of Dicumarol Therapy and Average Total Dose of Dicumarol Received by Each Group during the First Week of Dicumarol Therapy

Average Number of Seconds Prolongation of Whole Plasma Prothrombin Time[a] (Converted)[b] 3rd through 9th Day of Dicumarol	Cases with Usable Records[c] Receiving Dicumarol Nine Days or More		
	Number of Cases	Percentage of Cases	Average Total Dose of Dicumarol during First Week of Dicumarol (in mg.)
0 – 3 9	36	8	753
4 0– 7.9	113	26	812
8 0–11.9	100	23	827
12 0–15 9	75	17	875
16.0–19.9	57	13	808
20.0–23.9	35	8	830
24 0–27 9	16	4	*850*
28.0–31.9	6	1	—[d]
32.0–35 9	2	—[e]	—[d]
Total usable cases[c]	410	100	823

Note: *Italics are used when averages quoted have less than 30 cases as a base since chance factors render such means particularly unstable.*

[a] Represents the arithmetic mean of the number of seconds by which the daily readings from the 3rd to the 9th day exceeded the last prothrombin reading immediately before dicumarol was begun Readings below 15 seconds were counted as 15 For shortcomings of the mean as a measure for prothrombin time increases, see footnote a, Appendix F Table 83.

[b] For method of conversion, see pp. 350–352.

[c] No increase was computed for 169 cases for one or more of the following reasons: 1) less than 4 readings [illegible] not be converted (see footnote c, Appendix F Table 78); 4) dicumarol therapy was terminated or patient died before 9th day of illness, 5) no initial reading was available that was suitable for a base for computing the increase. Counts include control cases receiving dicumarol after the development of thromboembolic com-

68 never reached 30 seconds and 23 never reached even 25 seconds. *The price of this delay in prolongation is reflected in the data on thromboembolic complications occurring during anticoagulant therapy as given in Chapter VIII.*

Table 144, Appendix F Table 81, and Figure 151 analyze the initial rise in relation to dosage from a slightly different angle, namely, in relation to *total dosage* during the first three days. The relation of the higher doses to a more rapid climb to seconds within the optimal therapeutic range is here somewhat more evident in spite of the tendency of physicians to increase the dose when the initial response was low. Sixty per cent or less of each subgroup of patients receiving total doses in the first three days of less than 500 mg. reached 25 seconds by the 5th day, whereas 93 per cent of those who received 800 to 900 mg. in the period reached 25 seconds by the 5th day. The general relation of delayed response to low total dosage is also roughly apparent in Figure 151. The lack of adequate doses is indicated by the fact that by the 8th day, 12 per cent of the patients had not yet reached 25 seconds. Initial doses larger than those actually given were clearly needed in most cases for speedy and optimal protection.

Of the variety of initial doses received, those totalling 400 to 700 mg. in the first three days were most typical. The range of individual variations was wide. More than 40 patients received 800 to 900 mg. in this period, while 65 received less than 400 mg. These variations reflect both differences in policy and differences in the patients' response patterns.

Table 145 and Appendix F, Table 82 extend the dosage period studied to include the entire first week. When 7 instead of 3 days are included, the average total dose becomes 823 mg. About half the patients re-

INITIAL DOSAGE IN RELATION TO TIME REQUIRED TO REACH PROTHROMBIN TIME OF 25 SECONDS

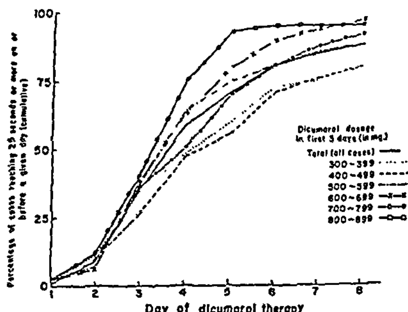


Figure 151. INITIAL DOSAGE IN RELATION TO TIME REQUIRED TO REACH PROTHROMBIN TIME OF 25 SECONDS: Cumulative percentage of cases receiving dicumarol and having usable records who reached prothrombin times of at least 25 seconds (23 per cent or less) on or before specific days of dicumarol therapy, by dosage received during first three days.

be considerably less, as demonstrated in Table 147, which reports the number of patients receiving dicumarol for more than one week who received various average daily doses of dicumarol. These averages were computed for each case by dividing the total amount of dicumarol received by the total number of days each patient was under the influence of dicumarol, excluding days after the last dose. The detailed counts appear in Appendix F, Table 83. On this basis the average daily dose was 85 mg. and the modal, or most usual, dose between 70 and 79 mg., a figure characteristic of 16 per cent of the 609 patients covered by the tabulation.

Differences between patients were again striking. One patient received an average daily dose of only 30 to 39 mg. and still showed prothrombin times averaging 25 to 29 seconds after the third day, while another patient responding with approximately the same times, received an average of 140 mg daily. Another case, particularly noteworthy for resistance to dicumarol, received 8500 mg of dicumarol in 14 days, or more than 600 mg. daily, although his average prothrombin time remained less than 20 seconds. *Since an individual's resistance cannot be measured in advance of actual trial, suitable dosage schedules for individuals cannot be determined from statistical tables. Such data can be useful only as a general guide for the average patient, from which frequent departures must be made in adjustment to individual differences.*

Table 147 and Figure 153 supported by Appendix F, Table 83 demonstrate strikingly the lack of any relation for the group as a whole between average daily dose and average prothrombin time. The proportion of patients having average times within various ranges does not change as average doses increase (see Figure 153 and Table 147); neither does the average daily dose increase appreciably as average prothrombin times increase until average prothrombin times of 40 seconds or more are reached (see Table 148). One must conclude that while the increase in prothrombin times are obviously progressively prolonged in most individuals as the dose is increased, when cases are grouped by dosage, they reflect also the counterbalancing tendency of physicians to increase the dose for those showing minimal response and to decrease the dose for those showing excessive response. As a result, the expected individual effect is masked.

Again, conclusions are warranted only with regard to the group as a whole. It is clear that the doses received, which averaged

TABLE 147

AVERAGE DAILY DOSE OF DICUMAROL: Number and Percentage of Cases Receiving Dicumarol More than One Week Who Received Various Average Daily Doses of Dicumarol and the Percentage of Each Dosage Class Maintained at Average Prothrombin Times of 25 Seconds or More

Dosage Group (Average Daily Dose of Dicumarol Received, in mg.)[a]	Cases Receiving Dicumarol More Than One Week[b]		Percentage of Dosage Group with Average[c] Prothrombin Times[d]—		
	Number of Cases	Percentage of Total Cases	Below 25 Seconds	25-34 Seconds	35 Seconds or More
Less than 50	35	6	40	36	24
50-69	135	25	35	50	15
70-89	169	31	27	53	20
90-109	114	21	31	45	24
110 and over	90	17	28	49	23
Total cases	543	100	31	49	20

[a] Averages are arithmetic means based on entire period of therapy. Means were not computed for cases treated less than one week because of the short period of therapy and the undue influence of heavy initial doses

[b] Counts include control cases receiving dicumarol but exclude cases receiving heparin only.

[c] Each case classified according to the arithmetic mean of all convertible prothrom[illegible] ...entages. For further specifications and disadvantage of means in this case, see footnote a of Appendix F Table 83.

[d] Converted For method of conversion, see pp. 350-352.

this basis the increase in response by dosage level becomes evident. The proportion of inadequately protected cases was greatest among those receiving less than 600 mg. during the first week and next greatest among those receiving 600 to 799 mg. The *two highest dosage groups* showed the smallest proportion of inadequate protection, with essentially no difference between them, the very high doses being apparently counteracted by their application to a more resistant group. When all are considered together, it is clear that nearly seven-tenths of the patients would have needed sub- stantially higher doses during this first week to assure that all or nearly all readings from the 3rd to the 9th day were 25 seconds or more. If this group is assumed typical in its dicumarol response, as seems probable, *an average dose during the first week of 823 mg. or more than 100 mg. daily, may be defined as inadequate for the majority of patients for the initial period.*

plications but exclude cases receiving heparin only.

[d] Not reported since there were fewer than 10 cases in the group.

[e] Less than .5 of 1 per cent.

Relation of Dosage to Maintenance Level of Prothrombin Time

The large amounts of dicumarol used in this early period obviously reflect the dosage required to secure the initial prolongation. *The average daily dose over the long term of*

TOTAL DICUMAROL DOSAGE IN FIRST WEEK AND PROTHROMBIN TIME RESPONSE

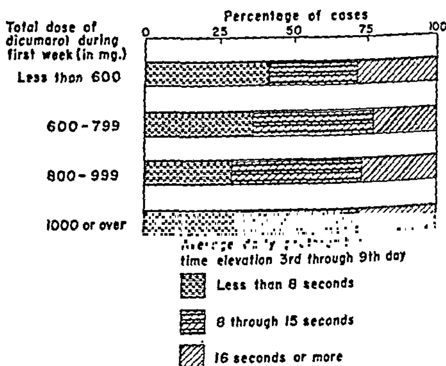


Figure 152. TOTAL DICUMAROL DOSAGE IN FIRST WEEK AND PROTHROMBIN TIME RESPONSE: Percentage of cases who received various total amounts of dicumarol during the first week of dicumarol therapy who showed an average number of seconds increase in prothrombin times of various amounts from the third through the ninth day of dicumarol therapy. (Totals exclude cases receiving dicumarol less than 9 days and cases for whom the prothrombin elevation could not be computed.)

into four groups according to the amount of response to given doses. The degree of reaction was difficult to appraise adequately under the circumstances prevailing, particularly since the available measures were relatively unrefined. Any particular response is a function not only of the patient's physiological response pattern but also of the amount and timing of doses received, the amount and timing of previous doses, prothrombin levels at the time specific doses were administered, the timing of prothrombin tests, delayed reactions, and numerous other factors.

These complexities and practical difficulties set important limits to the accuracy with which reaction patterns could be identified. Classification was based, where possible, on the average number of seconds increase in prothrombin time from the 3rd through the 9th day of dicumarol therapy produced by given total amounts of dicumarol received during the first week of anticoagulant therapy,[b] since the record for this period was considered the least affected by dosage adjustments by the physician to the patient's reaction pattern.

In order that patients' reactions to dicumarol might be compared only with those of other patients receiving somewhat similar doses of dicumarol in similar timing sequences, the hospitals with suitable records were divided into four groups primarily on

[b] *The average prolongation for each case computed for Table 146 and Appendix F, Table 82 was divided by the dose total for the same case as computed for these same tables. For the coverage and procedures, see the footnotes accompanying these tables.*

TABLE 148

AVERAGE PROT... Receiving Dicur... Time Levels f... ...eceived by Each Subgroup

Average[a] Prothrombin Time (Converted)[b]		Cases Receiving Dicumarol More than One Week[c]		
In Seconds	In Per Cent Prothrombin Activity	Number of Cases	Percentage of Cases	Average Daily Dose of Dicumarol Received[d] (in mg.)
15.0–17.9	100–52%	8	2	—[e]
18.0–19.9	51–37	23	4	*98*[f]
20.0–22.9	37.5–26.9	62	12	80
23.0–24.9	26.8–22.6	66	13	84
25.0–29.9	22.5–16.3	148	29	83
30.0–34.9	16.25–12.81	106	20	85
35.0–39.9	12.80–10.58	69	13	84
40.0–44.9	10.57–8.89	32	6	94
45.0 and over	8.88 and under	6	1	—[e]
Total cases with known prothrombin times		520	100	85

Note: *Italics are used when averages quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] See footnote c of Table 147.

[b] For method of conversion, see pp. 350–352.

[c] Counts include control cases receiving dicumarol but exclude cases receiving heparin only.

[d] Averages are arithmetic means of means for individual cases, the individual means being combined with equal weights for the entire period of therapy. Computations exclude cases treated for less than a week because of the excessively short period of therapy.

[e] Not computed since there were few...

[f] Average was greatly raised by c...

85 mg. daily for all persons treated more than one week and having known average times, erred on the side of being too low rather than too high in most cases. Only 6 cases treated more than one week showed averages in excess of 45 *seconds* while 159 cases showed averages of less than 25 seconds. These low averages prevailed in spite of the excessive influence that a few very high readings can have on the arithmetic average expressed in seconds for data taking the form of the prothrombin time dilution curve.[a] *The benefits attributed to anticoagulant therapy in this report are, therefore, those possible despite suboptimal therapy as reflected by the prothrombin time levels maintained.*

[a] See footnote f of Appendix F, Table 79.

CONDITIONS AFFECTING DEGREE OF RESPONSE TO DICUMAROL

Because of the clinical value to the patient of prompt and adequate prolongation of the prothrombin time without a preliminary experimental period, it would be of considerable practical utility to be able to identify in advance which patients might be unusually resistant to dicumarol and which might overreact. For this reason, a series of special analyses of the degree of reaction to dicumarol in relation to other conditions was undertaken.

Method of Classifying Degree of Reaction

The first step in this analysis was the classification of cases receiving dicumarol

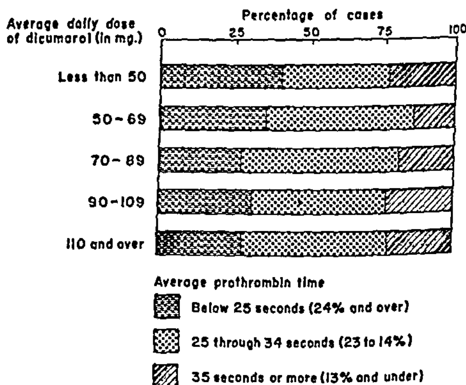


Figure 153. AVERAGE DICUMAROL DOSAGE IN RELATION TO AVERAGE PROTHROMBIN TIME: Percentage of cases receiving various average daily doses of dicumarol who were maintained at various average prothrombin levels from the fourth day of therapy through the day of the last dose.

ı of initial increase, classifications were ed where possible on the average number seconds in excess of 15 from the 4th day therapy through the day of the last dose t milligram in the average daily dose of umarol. Procedures thereafter were simi- : to those for cases with initial increase cords except that with certain minor ex- ptions hospital subgroups were not taken to account. In this manner an additional cases were classified and added to the action groups. To the total were added a w obvious high reactors with very brief cords The remaining 74 cases receiving nticoagulants could not be classified as to he degree of their reaction to dicumarol, or eceived heparin only. The final groupings nust be considered approximate only and ised with caution since slight changes in the lassification procedures would have altered lassifications in a number of instances.

Age

The first of the special tabulations based on these degree groups concerned average age and was designed to test roughly whether any relationship between age and degree of dicumarol response was apparent. The group with the minimum response showed an average age of 57.5; that with a maximum response, 59.2 years; the low middle reaction group, 56 3 years; and the high middle reaction group, 59.6 years. *These averages show no consistent relation between age and the degree of dicumarol response.* The analysis was not pursued further since it did not seem probable that a more refined type of analysis would reveal any relationship of dicumarol response to age.

Weight

The second possible relationship tested, namely, that with overweight and under-

DEGREE OF RESPONSE TO DICUMAROL
AND WEIGHT STATUS

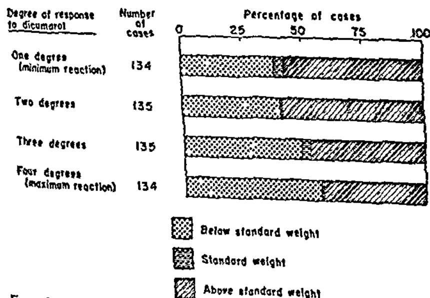


Figure 154. DEGREE OF RESPONSE TO DICUMAROL AND WEIGHT STATUS: Percentage of cases with various degrees of response to dicumarol having body weights below, the same as, and above standard weight levels for their age, sex, and height.

the basis of their similarity in the mean prothrombin times maintained during therapy. Within each hospital subgroup, patients were grouped into four subgroups according to the total amount of dicumarol they received during the first week of dicumarol. Reactions were judged only in relation to those of others in these relatively homogeneous subgroups.

Patients within each more or less homogeneous dosage subgroup were arranged in ascending order according to the average number of seconds increase in their prothrombin time from the third through the ninth day of anticoagulants. The fourth of the patients with the least reaction were said to show one degree of reaction to dicumarol; the second fourth with next to the least reaction, two degrees; those in the third fourth showing next to the top reaction, three degrees; and those in the fourth group (i.e., with the largest increases), four degrees of reaction. This division of a group into four subgroups in ascending order by a given measure is technically known as dividing the group into "quartiles." Finally, all reactors of similar degree from all subgroups were *considered to* belong in the same major reaction group. A total of 440 cases could thus be classified on the basis of their response from the third to the ninth day of anticoagulant therapy.

When *data* were lacking for the computa-

TABLE 149

DEGREE OF REACTION TO DICUMAROL IN RELATION TO WEIGHT: Number and Percentage *of Cases Showing Various Degrees of Reaction to Dicumarol Who Were Underweight, Average Weight, or Overweight for Their Height, Age, and Sex*

Weight Status	Total Cases with Known Reaction[a]	Degree of Reaction to Dicumarol[a] (Minimum Reaction ← → Maximum Reaction)			
		1 Degree (First Quartile—Group with Minimum Reaction)	2 Degrees (Second Quartile)	3 Degrees (Third Quartile)	4 Degrees (Fourth Quartile—Group with Maximum Reaction)
	Number of Cases				
Below standard weight	176	35	38	47	56
Standard weight	10	4	1	4	1
Above standard weight	191	51	53	46	41
Total cases with known weight	377	90	92	97	98
Weight unknown	161	44	43	38	36
Total cases in reaction subgroup	538	134	135	135	134
	Percentage of Cases[a]				
Below standard weight	47	39	41	49	57
Standard weight	2	4	1	4	1
Above standard weight	51	57	58	47	42
Total cases with known weight	100	100	100	100	100

... are excluded, but ... analysis ... y.

• Based on totals for whom relation to normal weight could be ...

e degree of dicumarol response would yield a fference between underweight and overweight rsons that was clearly significant statisti- lly This does not mean that the response f any particular patient can be predicted n the basis of weight.

Weight in this analysis, it should be noted, as tabulated in relation to normal weight ables that took into account the sex, height, nd age of each patient. Doses were not re- luced to mg. per kilo of body weight. Tabu- ations of reaction patterns classified in erms of mg. of dicumarol used per kilo of body weight, instead of in terms of weight n relation to a normal standard, might yield quite different results.

A further suggestion that the dicumarol response is related to the body intake and utilization of fat is contained in the findings on the association between cholesterol levels and dicumarol response, as shown in Table 150 and Figure 155. Of those with a minimum reaction to dicumarol, 44 per cent had cholesterol readings above normal and only 7 per cent, cholesterol levels below normal. In contrast, among those with a maximum dicumarol reaction, only 28 per cent were above normal in cholesterol readings, while 12 per cent were below normal in cholesterol. Unfortunately the number of cases in each response group with a known cholesterol reading is small and for samples of this size the observed difference between the minimum and maximum response groups is not statistically significant. However, the gradual downward trend in cholesterol level from the first to the fourth response group, as roughly reflected in Figure 155, is fairly consistent and the relationship, medically reasonable. One might be justified in specu-

DEGREE OF RESPONSE TO DICUMAROL
AND CHOLESTEROL LEVEL

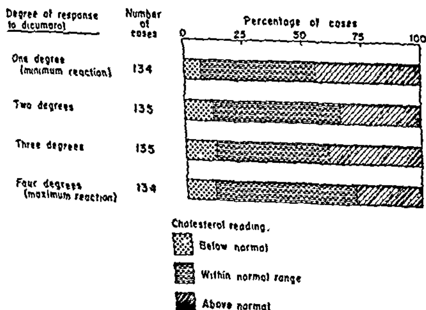


Figure 155. DEGREE OF RESPONSE TO DICUMAROL AND CHOLESTEROL LEVEL: Percentage of cases with various degrees of response to dicumarol whose cholesterol readings were below, within, or above the ranges reported as normal for the hospitals in question.

weight, resulted in more positive findings. The findings are given in Table 149 and Figure 154, in which cases are classified according to whether they were below, the same as, or above, standard weight for their height and age. Of those with a minimum reaction to dicumarol, 39 per cent were below normal in weight and 57 per cent, above normal. For those with a maximum reaction, the proportions were approximately the reverse, 57 per cent being underweight and 42 per cent, overweight. Although these differences are conspicuous, they are only of borderline significance statistically since the size of the sample in each reaction group is small, namely, 134 or 135 cases, and some in each group are without a report of weight. A difference as great as this would occur on a chance basis about 2 times in 100 samples of the same size from the same universe. It is likely that the relationship is actually a real one since it is consistent with the observation that malnutrition and low-fat diets may be associated with a deficiency in the body supply of vitamin K, a fat-soluble vitamin.[1] With a reduced supply of vitamin K, one would expect an exaggerated response to dicumarol and vice versa. *Probably a larger sample and a more precise measure of*

[1] See Marple and Wright,[m] pp 99–103

TABLE 150

DEGREE OF REACTION TO DICUMAROL IN RELATION TO CHOLESTEROL LEVEL: Number and Percentage of Cases among Those Showing Various Degrees of Reaction to Dicumarol Whose Cholesterol Readings Were below Normal, Normal, and above Normal Cholesterol Levels

Cholesterol Reading: Level in Relation to Normal Range for Hospital Reporting[a]	Total Cases with Known Reaction[b]	Degree of Reaction to Dicumarol[c] (Minimum Reaction → Maximum Reaction): 1 Degree (First Quartile—Group with Minimum Reaction)	2 Degrees (Second Quartile)	3 Degrees (Third Quartile)	4 Degrees (Fourth Quartile—Group with Maximum Reaction)
	Number of Cases				
Below normal	29	4	8	8	9
Within normal range	137	27	36	30	44
Above normal	92	24	23	24	21
Total cases with readings	258	55	67	62	74
Cases with no readings	280	79	68	73	60
Total cases in reaction subgroup	538	134	135	135	134
	Percentage of Cases[d]				
Below normal	11	7	12	13	12
Within normal range	53	49	54	48	60
Above normal	36	44	34	39	28
Total cases with readings	100	100	100	100	100

[a] See footnote a of Table 80. Patients were classified according to the least normal reading reporte

[b] See footnote a of Table 149.

[c] See footnote b of Table 149.

[d] Based on totals for cases with readings

should be undertaken with more than usual caution.

Diabetes

Table 151 and Figure 156 also report the egree of dicumarol response found in the l cases with diabetes whose degree of response could be classified. Twenty of these ases were found in the maximum quartile, 3 in the minimum quartile, 10 in the low middle quartile, and 8 in the high middle quartile. Thus, the response to dicumarol was sufficiently exaggerated in one direction or the other in 65 per cent of these diabetics to place them in the top or bottom response groups (as compared with an expected 50 per cent in these combined categories). While many more cases would be required to establish statistical significance for this finding, the discrepancy probably reflects an increased unpredictability in response in the case of diabetic patients. It provides a warning that patients with diabetes may offer more than usual problems in regulation under dicumarol although, without further research, this hypothesis must remain unproven.

Pneumonia and Bronchitis

Pneumonia and bronchitis were also sufficiently frequent as complicating conditions during the illness to be counted by response groups (see Figure 156 and Table 151). Nine of the 24 cases of pneumonia, bronchial pneumonia, and bronchitis that could be classified as to degree of dicumarol response fell in the maximum quartile for response, as compared with an expected number of six. While this discrepancy may well be due to chance, it may also be a reflection of the influence on dicumarol response of such factors as fever, infection, disturbed dietary regime, or change in liver or kidney function secondary to the infective process. The relation of degree of response to respiratory conditions is doubtless not a

DEGREE OF RESPONSE TO DICUMAROL IN RELATION TO AZOTEMIA, PNEUMONIA AND BRONCHITIS, AND DIABETES

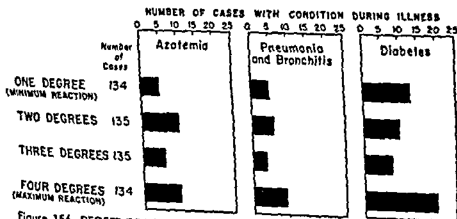


Figure 156. DEGREE OF RESPONSE TO DICUMAROL IN RELATION TO AZOTEMIA, PNEUMONIA AND BRONCHITIS, AND DIABETES. Number of cases with various degrees of response to dicumarol reported to have had azotemia during the six-week period of observation and corresponding data for pneumonia and bronchitis and for diabetes.

lating that a higher reserve of vitamin K, a fat-soluble vitamin, would be characteristic of patients having a high blood level of cholesterol-containing lipoprotein, a factor that would correlate, though roughly, with the level of plasma cholesterol. With larger samples in each reaction subgroup, a more precise measure of dicumarol response, comparable cholesterol tests, and a more detailed classification of cholesterol levels, a relationship with clear statistical significance might be established. The findings are sufficiently suggestive to warrant further research under carefully controlled conditions.

Liver Function

The relation of various pathological conditions to the degree of reaction to dicumarol was also explored by the same technique. Because of the known relation between liver function and dicumarol response,[j] a study of this response in cases with liver disease was of obvious interest. The opportunity to observe the relationship was, however, very limited, there being only 5 patients with known liver disease who received dicumarol therapy and could be classified as to the degree of their response to dicumarol. The diagnoses in these cases included jaundice, cancer of the liver, fatty liver, and liver disease of unclassified type. The remaining cases with liver disease in the series were control group cases, were considered unsuited to anticoagulant therapy, or could not be classified for some reason as to the degree of their response to dicumarol. The findings are reported in Table 151. Since only 5 cases with liver disease could be classified, the findings must be considered illustrative only. It is, nevertheless, typical of usual experience that 3 were in the group of maximum reactors. The high reactions in these 3 cases are consistent with the deficient synthesis of prothrombin (i e, deficient utilization of vitamin K) known to be associated with diseases of the liver in some instances.[k] As illustrated here by the 2 patients with liver disease who did not manifest this high reaction to dicumarol, *a maximum reaction to this drug is not uniformly characteristic in patients with liver disease, but caution should be observed in administering dicumarol to such patients in all instances.*

Renal Disease and Azotemia

Renal conditions and azotemia were also analyzed in relation to anticoagulant response, but the conclusions are obscure The findings are presented in Table 151 and Figure 156. Of the 31 patients showing azotemia at some time during their illness who could be classified with respect to dicumarol response, only 10 were in the group showing maximum dicumarol response. Seven of the 17 cases with other types of renal conditions also were in this maximum response group. In both groups the proportion of high reactors exceeds the expected one-fourth, but not to a dramatic degree. The remaining cases in the foregoing groups showed a variety of degrees of response including some of minimal degree Further study of responses in relation to the specific type of renal disease present was not feasible because of the small numbers, the variety of diagnoses, and the inadequate reporting of renal diagnoses. Though the numbers are small, these findings offer some further evidence in support of the clinical impression previously reported in the literature that the response to dicumarol in the presence of renal disease is unpredictable and may be excessive.[l] *For this reason dicumarol therapy in the presence of renal disease, though not necessarily contraindicated,*

[j] See Marple and Wright,[122] pp 99–103.

[k] See Marple and Wright,[122] pp. 100–105, 271–272

[l] See Marple and Wright,[122] pp. 109, 156–157.

group, the proportion of such cases with this degree of reaction was not excessive and no trend in the proportion of such cases was in evidence when the reaction groups were examined in sequence. One must conclude that the findings of the present study fail to show any consistent association between these conditions and the degree of reaction to dicumarol.

This result contrasts with those of Reisner et al[199] who found that the reaction to dicumarol frequently increased in patients with congestive heart failure and liver disease. Possibly the explanation lies in the the use in the present study of whole plasma to measure the response, for Stats and Davison[229] have found that the increased response in the presence of moderate to severe heart failure was apparent only when dilute (12.5 per cent) plasma was used. Further refinement of the analytic procedures for the present study might also have explained the divergence.

Sodium Restriction

A related count of patients on a restricted sodium intake showed no differences of consequence by reaction groups. The percentage of those with a report on this point that were actually limited in sodium intake was between 38 and 42 per cent in all reaction groups. Since sodium intake is commonly limited in patients with actual or threatened heart failure, this finding is consistent with those preceding in regard to the absence of a clear effect of heart failure on the degree of response to dicumarol.

The factors affecting the degree of response to dicumarol require much further

DEGREE OF RESPONSE TO DICUMAROL
IN RELATION TO SHOCK, CONGESTIVE FAILURE,
AND LIVER ENLARGEMENT

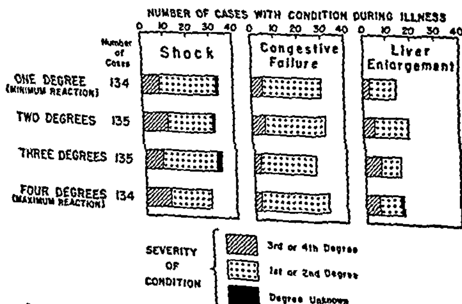


Figure 157. DEGREE OF RESPONSE TO DICUMAROL IN RELATION TO SHOCK, CONGESTIVE FAILURE, AND LIVER ENLARGEMENT: Number of cases with various degrees of response to dicumarol reported to have had shock during the six-week period of observation and corresponding data for congestive failure and liver enlargement.

specific one since some cases with these conditions appear in all reaction groups.

Shock, Congestive Heart Failure, and Liver Enlargement

In addition to these specific diagnoses, cases showing shock, congestive failure, or liver enlargement during the illness period studied were tabulated according to the degree of their response to dicumarol. The findings appear in Table 151 and Figure 157. While some cases with a record of shock, congestive failure, or liver enlargement were found in the maximum reactor

TABLE 151

DEGREE OF REACTION TO DICUMAROL IN RELATION TO OTHER PATHOLOGICAL CONDITIONS: Number of Cases with Various Pathological Conditions during the Six-Week Period Observed Showing Various Degrees of Reaction to Dicumarol

Pathological Condition[a]	Total Cases with Known Reaction[b]	Degree of Reaction to Dicumarol[c] (Minimum Reaction ← → Maximum Reaction): 1 Degree (First Quartile—Group with Minimum Reaction)	2 Degrees (Second Quartile)	3 Degrees (Third Quartile)	4 Degrees (Fourth Quartile—Group with Maximum Reaction)
Liver disease, any type	5	1	—	1	3
Azotemia	31	5	10	6	10
Renal disease other than azotemia	17	2	6	2	7
Pneumonia, bronchial pneumonia, and bronchitis	24	5	6	4	9
Diabetes	51	13	10	8	20
Shock (maximum at any time):					
First or second degree	87	25	20	24	18
Third or fourth degree	38	8	11	8	11
Degree unknown	4	1	1	2	—
Total with any shock	129	34	32	34	29
Congestive failure (maximum at any time)[d]:					
First or second degree	104	25	26	24	29
Third or fourth degree	17	5	6	3	3
Total with any congestive failure	121	30	32	27	32
Liver enlargement (maximum at any time):					
First or second degree	42	11	14	8	9
Third or fourth degree	21	3	5	7	6
Degree unknown	1	—	—	—	1
Total with any liver enlargement	64	14	19	15	16
Total cases in reaction subgroup..	538	134	135	135	134

[a] Records of dates were not sufficiently complete or detailed to permit a precise delineation of the time a given condition developed in relation to the time a given reaction to a given dose of dicumarol occurred. In a few cases, particularly those of shock, condition may not have been present during the period patient received dicumarol

[b] See footnote a of Table 149.

[c] See footnote b of Table 149.

[d] Excluding cases with initial congestive failure only (i e , congestive failure clearing by the third day).

ypical prothrombin time response to myo- [illegible] infarction in the absence of anticoag- [illegible] therapy. While prothrombin times were not actually reported with the regularity and frequency that had been hoped, [illegible] analyses were nevertheless attempted.

Prothrombin times obtained immediately following the attack were selected for particular attention. These times were compared with the distribution of test findings for normal persons used as controls and tested under corresponding laboratory conditions. Times for the treated group were also included in those instances where a reading before the beginning of anticoagulants was available. All were converted to the standardized curve by identical procedures and combined in such a way as to give each hospital the same proportional representation in the normal group as in the group for coronary thrombosis cases. The results are presented separately for whole plasma and for dilute plasma in the pages that follow.

Readings for Whole Plasma

The data suggest that some slight differences between the prothrombin times of coronary thrombosis cases shortly after the attack and those of normal persons probably do exist and that the differences are not of the same nature for whole as for dilute plasma. The mean and median prothrombin times for coronary thrombosis cases based on the first whole plasma readings after the attack were more prolonged than were corresponding measures for normal persons (see Table 152 and Figure 158), the differences in each case being sufficient to be highly significant statistically though hardly great enough to be clinically obvious or important.[m] As would be expected from these findings, the distribution curve for coronary thrombosis cases also lies slightly

[m] Tests throughout this section take into ac- [illegible]

AVERAGE PROTHROMBIN TIMES FOR WHOLE PLASMA WITHOUT ANTICOAGULANTS

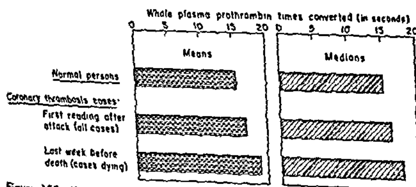


Figure 158. AVERAGE PROTHROMBIN TIMES FOR WHOLE PLASMA WITHOUT ANTICOAGULANTS. *Means and medians for all usable first prothrombin times for whole plasma for coronary thrombosis patients taken after the attack and before the beginning of anticoagulants, for similar readings for normal persons tested on the same day under the same laboratory conditions, and for readings taken during the last week before death for coronary thrombosis patients dying and having four or more prothrombin times taken during this last week (readings during anticoagulant therapy excluded).*

study before definitive conclusions can be reached. Observation of patients' responses *under defined conditions to single standard doses of this anticoagulant on the same day that other symptoms or conditions are* known to be present would seem to offer a better possibility of isolating the relevant factors than did the study of the long-term average response attempted in the present study.

Drugs

Certain drugs known to produce hypoprothrombinemia, notably *quinine*, *sulphonamides*, and large doses of salicylates, can also affect the response to dicumarol but demonstration of these effects was not attempted in the present study. Special watchfulness should be maintained when dicumarol is used in conjunction with these drugs. Similar care is indicated when the gut-sterilizing antibiotics, such as chloromycetin, terramycin, and aureomycin, are used since this sterilizing process interferes with the natural synthesis of vitamin K. Other drugs, notably adrenalin and penicillin, accelerate the prothrombin time. A review of the literature on the effects of certain drugs on the blood coagulation and on the prothrombin time is given in Marple and Wright.[113]

PROTHROMBIN TIMES OF CORONARY THROMBOSIS CASES IN THE ABSENCE OF ANTICOAGULANTS

Since the hospitals were requested to run prothrombin times on both control and treated patients, the resulting records from the control group provided an unusual accumulation of data with which to study the

TABLE 152

PROTHROMBIN TIMES OF CORONARY THROMBOSIS PATIENTS AND NORMAL PERSONS

[illegible]

Persons Tested under Corresponding Laboratory Conditions

Type of Measure and Plasma Concentration	Number of Usable Readings[a]	Prothrombin Time (in converted seconds)[b]: Coronary Thrombosis Cases, Total Sample in the Present Series (1st Reading after Attack): Value	Standard Error	Normal Persons (Tested under Corresponding Laboratory Conditions)[c]: Value	Standard Error
Undilute prothrombin times.					
Mean	523	16.92	±.12	15.45	±.07
Median	523	16.40	±.15	15.20	±.08
Standard deviation	523	2 78	±.09	1.25	± 05
Dilute prothrombin times:					
Mean	342	34 98	±.44	35.22	±.35
Median	342	33 22	±.55	35.36	±.44
Standard deviation	342	8 11	± 31	4 68	±.25

[a] Readings influenced by anticoagulants were not considered usable. For distributions of readings and further specifications, see Appendix F Tables 84 and 85 and related footnotes

[b] For explanation of conversion procedure, see pp. 350–352.

[c] For method of compiling data for normal persons and actual number of available observations used in computing standard errors for normal persons, see footnote c of Appendix F Table 84 and footnote c of Appendix F Table 85.

cepted normal range or to attract attention clinically as hypoprothrombinemia cases.

Readings for Dilute Plasma (12.5 per cent)

For dilute plasma (12.5 per cent), the relationship is apparently the opposite. The details of the findings are presented in Table 152, Appendix F Table 85, and Figures 160 and 161. This time the distribution for coronary thrombosis cases as shown in Figure 161 lies to the left instead of to the right of that for normal persons, is flatter, and covers a considerably wider range In consequence of this greater dispersion, the standard deviation for dilute readings for the coronary thrombosis cases was also larger than that for normals in an amount that was statistically highly significant. In view of these differences, it is strange that the two means differed only very slightly and in an amount that is clearly not statistically significant. This anomaly appears to be due to the counterbalancing effect of a few markedly high readings on many low ones in the computation of the arithmetic average. The medians which are uninfluenced by such extreme values differed by two seconds, a statistically significant difference in this instance, the faster times being characteristic of the coronary thrombosis cases.

When each dilute reading for a coronary thrombosis patient was compared with its own control figure for the same day, and all readings without usable control times for the same day were omitted, the results were as shown in Table 153 and Figure 160. Fifty-two per cent of such readings were faster than their control time, 17 per cent

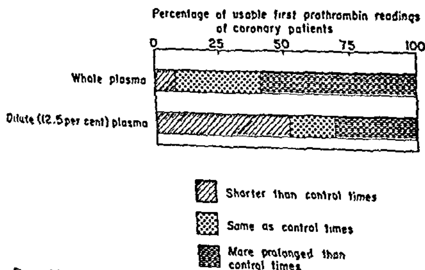


Figure 160. PROTHROMBIN TIMES OF CORONARY PATIENTS COMPARED WITH CONTROL TIMES: Percentage of all usable *first undilute* and dilute prothrombin readings taken *after* the attack and before the beginning of anticoagulant therapy (if any) that were shorter than, the same as, and more prolonged than the hospital control figure for the same day for normal plasma (times rounded to nearest whole second prior to comparisons).

to the right of that for normals, is flatter, and covers a wider range (see Appendix F Table 84 and Figure 159). This greater dispersion is reflected also in the standard deviation for the coronary thrombosis group, which is about twice as great as that for the normals. The difference is again highly significant statistically, but the medical meaning of this greater variability is not clear.

These differences in prothrombin time findings for whole plasma are further confirmed by Table 153 and Figure 160 in which each first reading for a coronary thrombosis case is compared individually (in terms of whole seconds) with its own control figure for the same day and classified as above, below, or the same as its control figure. Cases without a control figure for the specific day in question were omitted from this tabulation. Fifty-nine per cent of the first readings for coronary thrombosis patients in this series were more prolonged than their individual control figure, 33 per cent were the same as this figure, and only 8 per cent, faster than this figure. If there were no real difference, the proportions above and below would be expected to be about equal. The departure from this expected chance pattern is statistically highly significant in this instance. In spite of this fact, however, only a relatively small proportion of the readings were sufficiently prolonged to fall outside the upper limit of the usually ac-

PROTHROMBIN TIMES FOR WHOLE PLASMA FOR CORONARY THROMBOSIS PATIENTS AND NORMAL PERSONS

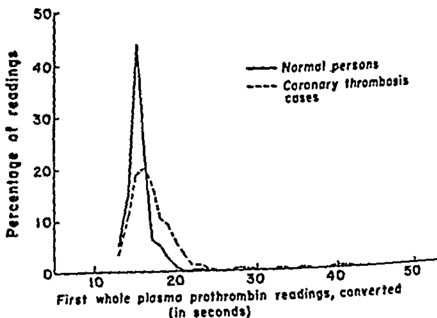


Figure 159. PROTHROMBIN TIMES FOR WHOLE PLASMA FOR CORONARY THROMBOSIS PATIENTS AND NORMAL PERSONS: *Percentage distribution of the first prothrombin time readings for whole plasma taken from patients in the sample after their original attack of coronary thrombosis and before the beginning of anticoagulant therapy and percentage distribution of corresponding prothrombin times for normal persons whose blood was tested under corresponding laboratory conditions (percentages of readings at 14 and 13 seconds are estimated).*

ttack, such as congestive failure, shock, nd vomiting unfortunately confuse the icture.

It is interesting and possibly significant hat, in the present study, hypoprothrombinemia rather than hyperprothrombinemia was typical of whole plasma following the attack. Similar prolongations for whole plasma prothrombin times have been observed by Beaumont, Chevalier, and Lenègre.[17] This prolongation stands in marked contrast to the hyperprothrombinemia characteristic of the same plasma diluted This contrast between whole and dilute findings is, moreover, consistent with the suggestion of Schilling and De Natale[312, 313] that "autoanticoagulant-like substance" is present within 24 hours of the onset of a myocardial infarction and continues "until it is resolved," producing a prolongation of the prothrombin time for whole plasma but having relatively "no effect on the 12.5 per cent plasma prothrombin time." It is also consistent with the position taken by Beaumont, Chevalier, and Lenègre[17] that a period of spontaneous hypocoagulability follows myocardial infarction beginning on the second day and continuing until the eighth or tenth day and is demonstrable both with the measurement of heparin tolerance *in vitro* and with the whole plasma prothrombin time.[a] Dilute plasma prothrombin times during this period became shorter or remained normal

The process of physiological response to thromboembolism could be better understood and described if prothrombin readings for the same individuals could be secured in enough instances both before and after an attack of coronary thrombosis. It is seldom possible, however, to predict the onset of such an attack sufficiently accurately to secure a reading immediately prior to its beginning. If it were possible to predict the onset of coronary thrombosis, the interests of the patient would suggest the use of anticoagulants prophylactically, with the consequent loss both of natural prothrombin readings thereafter and of the confirming evidence of the actual subsequent attack.

[a] These authors also observed that 24–48 hours after myocardial infarction the coagulation time, when measured by the heparin tolerance test, was very short but this brief period of hypercoagulability was not found reflected in the whole plasma prothrombin time.

TABLE 153

PROTHROMBIN TIMES OF CORONARY THROMBOSIS PATIENTS COMPARED WITH THEIR OWN CONTROL TIMES: Number and Percentage of Usable First Prothrombin Readings, Undilute and Dilute, Taken Prior to the Beginning of Anticoagulant Therapy (if Any) for the Total Sample Showing Times Faster than, the Same as, and More Prolonged than the Corresponding Hospital Control Readings for the Same Day

Relation of Patient's Prothrombin Time to Hospital Control Figure for the Same Day	Usable First Prothrombin Reading[a]			
	Undilute Plasma		Dilute Plasma (12.5 per cent)	
	Number	Per Cent[b]	Number	Per Cent[b]
Coronary thrombosis patient's first reading—				
Faster than control time	34	8	54	52
Same as control time	130	33	17	17
More prolonged than control time	233	59	32	31
Total readings with controls	397	100	103	100

[a] Readings were considered usable if they were taken on or before the first day of anticoagulant therapy provided the hospital control figure for the same day was reported and heparin was not

...the proportion of readings above the control figures for the day should be approximately the same as that below this figure.

were the same as such times, and only 31 per cent were more prolonged. Statistically, the departure from the expected even distribution if only chance factors were operating is of borderline significance, but in view of the other findings, is probably real. Since individual readings typically fall within normal limits, these small but quite consistent departures from control readings do not attract attention clinically.

The acceleration of dilute prothrombin times in coronary thrombosis cases following the attack has been demonstrated previously by Shapiro,[218] by Meyers and Poindexter,[159] by Peters, Guyther, and Brambel,[196] by Overman and Wright,[173] and by Beaumont, Chevalier, and Lenègre[17] but Tuft and Rosenfield[233] have not been able to detect such an acceleration of prothrombin time under these circumstances.

The underlying physiological mechanism of this apparent hyperprothrombinemia is not clear. The findings for dilute plasma may represent a reaction to the infarction or may be a continuation of the hyperprothrombinemia believed by Shapiro[218] and others[21,10] to characterize in some cases the developmental stage of intravascular thrombosis. The effects on whole prothrombin time of debilitating conditions accompanying the

PROTHROMBIN TIMES FOR DILUTE PLASMA FOR CORONARY THROMBOSIS PATIENTS AND NORMAL PERSONS

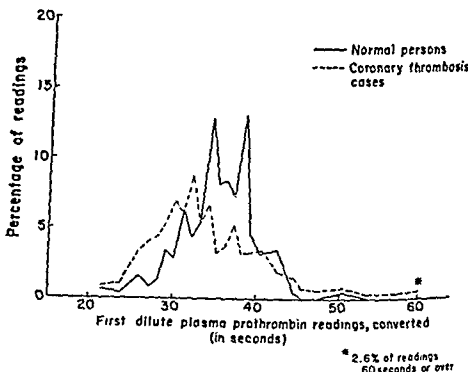


Figure 161. PROTHROMBIN TIMES FOR DILUTE PLASMA FOR CORONARY THROMBOSIS PATIENTS AND NORMAL PERSONS: Percentage distribution of the first prothrombin time readings for dilute (12.5 per cent) plasma taken from patients in the sample after their original attack of coronary thrombosis and before the beginning of anticoagulant therapy and percentage distribution of corresponding prothrombin times for normal persons whose blood was tested under corresponding laboratory conditions.

uld in the future be justifiable only with tients precluded from anticoagulant ther- y after very careful consideration of all :tors including contraindications. Pro- rombin times for such patients before and ter the development of thromboembolic mplications should provide a basis for the :lineation of the physiological sequence in rothrombin times involved. Such records ould also be useful in determining whether ıy trend in prothrombin times is apparent uring the course of the illness and healing rocess.

Prothrombin Times Prior to Death

In this study, the only analysis of pro- :hrombin times actually undertaken for control patients during the course of the ill- ness was that for cases dying. Since marked increases in the degree of response to anti- coagulant therapy were occasionally ob- served in moribund cases, the question was raised as to whether this was the usual se- quence prior to death. A review of available data disclosed 25 control patients who died during the period of study for whom 4 or more prothrombin readings for whole plasma were available during the week before death. The results of an analysis of these readings, reported in Table 154, Figure 158 and Fig- ure 162, showed a slightly higher proportion of prolonged readings during the last week than among first readings after the attack for all patients in the sample. The mean of

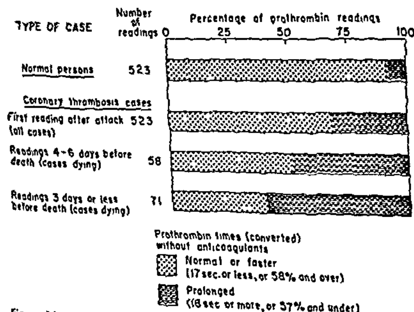


Figure 162. PROLONGED PROTHROMBIN TIMES FOR WHOLE PLASMA WITH- OUT ANTICOAGULANTS: Percentage of total available prothrombin readings for whole plasma for coronary thrombosis patients that were 18 seconds or more among all usable first readings taken after the attack, among readings for normal persons tested on the same day in the same laboratory, and among readings taken during two portions of the last week before death for coronary thrombosis patients dying (readings during anticoagulant therapy excluded).

Knowledge of the physiological prothrombin time sequence that precedes the development of thromboembolic complications subsequent to the initial attack would also be of considerable interest. Unfortunately, the great variation in the method, frequency, and periodicity of prothrombin readings for control patients reduced the number of instances of such complications followed by full prothrombin time records in the absence of anticoagulants to too small a sample to justify statistical treatment, and the variations in prothrombin times before and after the development of thromboembolic complications were too minor and random in character to make possible a description of the typical sequence merely from observation of individual case records. With the accumulated evidence of the value of anticoagulant therapy, such a study

TABLE 154

TRENDS IN PROTHROMBIN TIMES WITHOUT ANTICOAGULANTS DURING LAST WEEK BEFORE DEATH: Number of Cases Whose Prothrombin Times Fell at Various Levels during the Last Seven Days prior to Death and Daily Mean and Median Prothrombin Times for These Last Days among 25 Cases Receiving No Anticoagulants, Dying during the Period of Observation, and Having Four or More Prothrombin Readings Reported for This Last Week of Life

Prothrombin Time (Converted)[a]		Number of Prothrombin Readings[b]								Per Cent of Total Known Prothrombin Readings for Last Week before Death[b]
			Days before Day of Death							
In Seconds	In Per Cent Prothrombin Activity	Total Readings for Last Week	6	5	4	3	2	1	0 (Day of Death)	
Under 15	Over 100%	14	5	2	1	—	1	3	2	11
15–17	100–58	45	8	6	8	8	8	5	2	35
18–19	57–41	34	2	5	5	9	4	7	2	26
20–22	40–28.3	22	3	5	4	2	*1*	*5*	2	17
23–24	28.2–23.7	3	—	—	1	1	—	—	1	2
25–29	23.6–16.8	8	1	1	—	1	2	1	2	6
30–34	16.7–13.2	1	—	—	—	—	—	1	—	1
35–39	*13.1–10.9*	2	—	—	1	—	1	—	—	2
Total number of known readings[c]		129	19	19	20	21	17	22	11	100
		Averages[d]								
Mean of known prothrombin times		*19*	*17*	*18*	*19*	*19*	*19*	*19*	*20*	—
Median of known prothrombin times		18	*17*	*18*	*18*	*18*	*17*	*18*	*19*	—

Italics are used when averages quoted are based on less than 30 cases since chance factors render such figures particularly unstable.

[a] For method of conversion, see pp 350–352.

[b] Counts exclude cases not dying, cases receiving anticoagulants, and cases with fewer than 4 prothrombin readings reported for the last week prior to death.

[c] Days that are unknown and number of days unknown fluctuate from case to case; hence composition of samples fluctuates somewhat from day to day. The number of unknown readings daily is the difference between the total cited and 25. If the analysis had been limited to cases with seven readings during the last week, the size of the sample would have been totally inadequate.

[d] All averages are stated in terms of converted seconds and are based on ungrouped data.

would in the future be justifiable only with patients precluded from anticoagulant therapy after very careful consideration of all factors including contraindications. Prothrombin times for such patients before and after the development of thromboembolic complications should provide a basis for the delineation of the physiological sequence in prothrombin times involved. Such records would also be useful in determining whether any trend in prothrombin times is apparent during the course of the illness and healing process.

Prothrombin Times Prior to Death

In this study, the only analysis of prothrombin times actually undertaken for control patients during the course of the illness was that for cases dying. Since marked increases in the degree of response to anticoagulant therapy were occasionally observed in moribund cases, the question was raised as to whether this was the usual sequence prior to death. A review of available data disclosed 25 control patients who died during the period of study for whom 4 or more prothrombin readings for whole plasma were available during the week before death. The results of an analysis of these readings, reported in Table 154, Figure 158 and Figure 162, showed a slightly higher proportion of prolonged readings during the last week than among first readings after the attack for all patients in the sample. The mean of

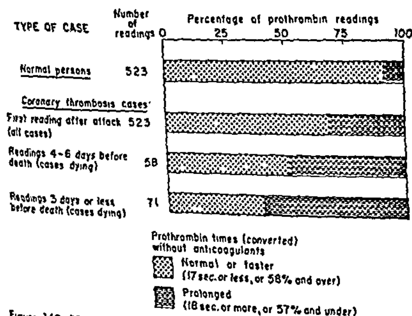


Figure 162. PROLONGED PROTHROMBIN TIMES FOR WHOLE PLASMA WITHOUT ANTICOAGULANTS- Percentage of total available prothrombin readings for whole plasma for coronary thrombosis patients that were 18 seconds or more among all usable first readings taken after the attack, among readings for normal persons tested on the same day in the same laboratory, and among readings taken during two portions of the last week before death for coronary thrombosis patients dying (readings during anticoagulant therapy excluded).

these readings for the last week was 19 seconds as compared to 16.9 seconds for the first readings after the attack. On the day of death the mean *increased to 20 seconds.* The trend on a daily basis for both the means and medians was *fairly consistent* (see Table 154). The proportion of readings that were 18 seconds or more reflects the *trend* more conspicuously than do the averages. Among normal persons used as *controls, only* 8 per cent had times of 18 *seconds* or more after conversion to the standardized curve. Among the 523 coronary *thrombosis* cases in the present series with a usable reading after the attack, 31 per cent had times of 18 seconds or more, converted. Of 58 usable readings taken 4 to 6 days before death among 25 cases dying, 48 per cent were 18 seconds or more, whereas during the terminal period (last 3 days before death plus day of death) 59 per cent of 71 *readings* were 18 seconds or more. The downhill course prior to death seems to be associated, at least among these coronary thrombosis cases, with a slight prolongation of prothrombin times for whole plasma. The factors responsible for this trend were not identified.

The last week prior to death was also studied for patients under anticoagulant therapy during this week. As in the case of control group patients, the study of the response in treated group patients prior to death was handicapped by the small samples available, the omission of readings for some days, and miscellaneous interhospital differences in testing and reporting times. Since the dosage of anticoagulants was not standardized or controlled, this influence further confused the picture of the operation of physiological factors prior to death for treated cases. The findings of this second analysis are therefore not reported in tabular or graphic form. Mean prothrombin times for 38 patients under anticoagulants during the last week before death and having 4 or more prothrombin times reported for these days ranged from a low of 26 seconds 5 days before death to a peak of 31 seconds on day of death. Medians for these same tients during the last week of life ran from a low of 23 seconds 6 days before de to a high of 28 seconds on the day of dea Obviously an upward trend in dicuma response prior to death, *if present,* is at le not marked in the average case. No parti lar condition could be identified with wh an exaggerated response to dicumarol pr to death was consistently associated. Mu remains to be learned about the effects various physiological conditions on pr thrombin times.

SUMMARY

The prothrombin times reported in co nection with this study were analyze statistically with the following results:

A. Findings relative to the relation o prothrombin time levels to thromboemboli complications and hemorrhages:

1. *The optimal therapeutic range for prothrombin times for whole plasma was defined as approximately 25 to 39 seconds, or 23 to 11 per cent prothrombin activity, since the minimum incidence of thromboembolic complications was not reached until prothrombin times were prolonged to at least 25 seconds, and since the incidence of hemorrhages related to anticoagulants increased rapidly as times were prolonged beyond 40 seconds.*

2. *The incidence of thromboembolic complications was lower on the third day of three-day sequences when all three prothrombin readings had been 30 seconds or more (16 per cent or less) than for similar periods in which the last reading was 30 seconds or more and one or both of the two previous readings were less prolonged* (i.e., 1.9 *vs.* 2.6 complications respec*tively).*

3. Patients receiving dicumarol therapy conforming to standards defined as "relatively ideal" showed a markedly lower incidence of thromboembolic *complications and*

a somewhat higher incidence of hemorrhages than did corresponding patients receiving dicumarol therapy classified as "clearly not ideal"

4. *The prothrombin time levels maintained during the study, as judged by these standards, were suboptimal for a substantial proportion of the cases included.* For example, 42 per cent of the days of dicumarol therapy with known times were reported to show times below 25 seconds *The marked improvement in the results of treatment of myocardial infarction with anticoagulant therapy was achieved in spite of these suboptimal standards. With therapy characterized by optimal prolongation, a still further improvement in the thromboembolic rate may reasonably be expected.*

B. Findings relative to the characteristics of dicumarol as an anticoagulant:

1. The delayed physiological response to dicumarol is reflected in a lag between the time dicumarol is first administered and the time the patient reaches the recommended minimum prolongation. Of patients with usable records, 41 per cent did not reach 25 seconds by the 4th day and 29 per cent did not reach this level by the 5th day. While increased initial doses accelerated the process slightly, a measure of lag was characteristic of all dosage levels.

2 A similar lag occurred after the termination of dicumarol therapy. Those with usable terminal records required an average of 4 days after the last dose of dicumarol before their prothrombin times returned to 17 seconds or less, while 12 per cent required 7 days or more.

3. Since the prothrombin times achieved were on the whole suboptimal, the doses received by the average patient may be assumed to be too low The average total dose during the first week was actually 823 mg. The average daily doses for patients treated with dicumarol more than one week averaged 85 mg. Although these amounts are clearly too low, it is not possible to determine from the records how much increase in these averages would be required for optimum results with patients of these types.

4. Large and unpredictable differences were observed in the prothrombin levels produced with given amounts of dicumarol. These differences confuse the statistical picture and render it impossible to define *a priori* dosage schedules that will be adequate for given individuals.

5. Minimal responses to dicumarol were found in more than the expected proportion of patients who were overweight or had high cholesterol readings, but the departures from the expected were not clearly statistically significant, possibly because of the small samples available. Findings on associations between other conditions and dicumarol response were negative, mixed in character, or indeterminate.

C. Findings on prothrombin time levels in the absence of anticoagulants:

1. In comparison with normal persons used as controls, coronary thrombosis patients in this study in their first readings after the attack showed on the average a very slight but statistically significant prolongation of whole prothrombin times and an opposite acceleration of dilute prothrombin times.

2. In comparison with these first readings after the attack for all patients, moribund patients showed a slight further prolongation in whole prothrombin times in the last days prior to death

these readings for the last week was 19 seconds as compared to 16.9 seconds for the first readings after the attack. On the day of death the mean increased to 20 seconds. The trend on a daily basis for both the means and medians was fairly consistent (see Table 154). The proportion of readings that were 18 seconds or more reflects the trend more conspicuously than do the averages. Among normal persons used as controls, only 8 per cent had times of 18 seconds or more after conversion to the standardized curve. Among the 523 coronary thrombosis cases in the present series with a usable reading after the attack, 31 per cent had times of 18 seconds or more, converted. Of 58 usable readings taken 4 to 6 days before death among 25 cases dying, 48 per cent were 18 seconds or more, whereas during the terminal period (last 3 days before death plus day of death) 59 per cent of 71 readings were 18 seconds or more. The downhill course prior to death seems to be associated, at least among these coronary thrombosis cases, with a slight prolongation of prothrombin times for whole plasma. The factors responsible for this trend were not identified.

The last week prior to death was also studied for patients under anticoagulant therapy during this week. As in the case of control group patients, the study of the response in treated group patients prior to death was handicapped by the small samples available, the omission of readings for some days, and miscellaneous interhospital differences in testing and reporting times. Since the dosage of anticoagulants was not standardized or controlled, this influence further confused the picture of the operation of physiological factors prior to death for treated cases. The findings of this second analysis are therefore not reported in tabular or graphic form. Mean prothrombin times for 38 patients under anticoagulants during the last week before death and having 4 or more prothrombin times reported for these days ranged from a low of 26 seconds 5 days before death to a peak of 31 seconds on the day of death. Medians for these same patients during the last week of life ranged from a low of 23 seconds 6 days before death to a high of 28 seconds on the day of death. Obviously an upward trend in dicumarol response prior to death, if present, is at least not marked in the average case. No particular condition could be identified with which an exaggerated response to dicumarol prior to death was consistently associated. Much remains to be learned about the effects of various physiological conditions on prothrombin times.

SUMMARY

The prothrombin times reported in connection with this study were analyzed statistically with the following results:

A. Findings relative to the relation of prothrombin time levels to thromboembolic complications and hemorrhages:

1. *The optimal therapeutic range for prothrombin times for whole plasma was defined as approximately 25 to 39 seconds, or 23 to 11 per cent prothrombin activity, since the minimum incidence of thromboembolic complications was not reached until prothrombin times were prolonged to at least 25 seconds, and since the incidence of hemorrhages related to anticoagulants increased rapidly as times were prolonged beyond 40 seconds.*

2. *The incidence of thromboembolic complications was lower on the third day of three-day sequences when all three prothrombin readings had been 30 seconds or more (16 per cent or less) than for similar periods in which the last reading was 30 seconds or more and one or both of the two previous readings were less prolonged* (i.e., 1.9 vs. 2.6 complications respectively).

3. Patients receiving dicumarol therapy conforming to standards defined as "relatively ideal" showed a markedly lower incidence of thromboembolic complications and

group, as previously defined (see Chapter III). Thus, two control cases (even-day cases) examined at autopsy who had received anticoagulants following the development of a thromboembolic complication are classified in the autopsy tabulations as "cases receiving anticoagulants." Also, three treated cases (odd-day cases) who did not at any time receive anticoagulants are classified in the autopsy tabulations as "cases not receiving anticoagulants." Finally, two cases in the treated group examined at autopsy are omitted from most autopsy tabulations since no recent coronary occlusion and no recent myocardial infarction was recognized postmortem. It is impossible to determine in detail the types of selection, if any, that resulted from these switches. Since only a few cases were involved, it is doubtful that the rearrangement affected the general conclusions.

As a consequence of these switches and omissions, the 419 cases in the total sample that received no anticoagulants at any time are represented in the autopsy sample by 48 cases and the 612 that received anticoagulants are represented by 41 cases. It should be noted that the rearrangement changes not only the autopsy case counts but also the treatment group counts for the total series. Since some especially severe control group cases received anticoagulants out of turn, the rearrangement results also unavoidably in some loss of equality in the base groups with consequences for the findings that are unknown. Fortunately, inequalities in the base groups thus defined are automatically reduced by the omission of nondeaths from the autopsy sample and thus may be negligible for purposes of evaluation

Completeness of the Autopsy Examinations

Gross Reports

The percentage of autopsy protocols that included gross and microscopic reports on the findings for given organs are summarized in Figure 163 and reported in detail in Appendix F, Table 86. Appendix F, Table 87 shows the proportion of organ reports that were descriptive in form. Of the organs examined grossly, 88 per cent were actually described in the reports submitted. In the remaining instances the reports gave summaries of the findings but lacked descriptive detail. Descriptions were included for 92 per cent of the organs examined in cases receiving anticoagulants as contrasted with only 85 per cent of the organs examined for cases receiving no anticoagulants (see Appendix F, Table 87). The somewhat fuller reports for the treated cases would perhaps lend a slight upward bias to the thromboembolic and hemorrhagic findings for the treated group, a result that would in turn reduce slightly the impression of benefit from therapy.

The organs examined varied widely from case to case. Only the heart was examined grossly in every instance. However, the lungs, liver, kidney, aorta, spleen, pancreas, adrenals, prostate, uterus, and gastrointestinal tract were examined in 84 per cent or more of the cases. Since permission for autopsy was granted on a limited basis only in some instances, these percentages seem reasonably satisfactory. The low percentage of cases in which the brain was examined, namely, 37 per cent, was disappointing. This low percentage is undoubtedly related to the frequent restrictions imposed by families who fear disfiguration of the body. The possible frequency of changes in the brain resulting not alone from thromboembolic phenomena, but from cerebrovascular changes in general is naturally cause for regret that this organ was not examined in a higher percentage of cases.

The very low percentage of instances in which the vessels of the legs were examined at autopsy (only 10 per cent including "milking" and "fishing") is also regrettable. Since the veins of the legs are generally considered to be the most common site for the development of venous thrombosis (including the frequently unrecognized so-called "benign phlebothrombosis") and the most

Autopsy Findings

A CORRECT evaluation of anticoagulant therapy in coronary occlusion with myocardial infarction requires a review of autopsy findings for a number of reasons: (1) some of the consequences of coronary occlusion, such as intracardiac mural thrombosis and some instances of cardiac rupture, cannot be identified clinically; (2) other thromboembolic complications may be unreported because they do not produce clinically recognizable syndromes or because the clinical findings are not correctly interpreted; and (3) some hemorrhagic complications may be too minor or hidden to be detectable clinically. Thus, by disclosing clinically unrecognized developments, autopsy studies provide a more precise determination of the effect of anticoagulant therapy on thromboembolic and hemorrhagic complications. They also afford a measure of the accuracy of the clinical diagnosis of thromboembolic complications, of the location, extent and etiology of the original infarction, and of other clinical findings. These observations may obviously be applied only to patients who died and were autopsied.

All cooperating hospitals were therefore requested to forward to the Central Laboratory a copy of the full autopsy report, including the microscopic findings, for each case in the series examined postmortem. These records were reviewed by the medical staff of the project and analyzed statistically, particularly with reference to the thromboembolic complications and hemorrhages found. This chapter presents the findings of this analysis with regard to the following topics: (1) the frequency and completeness of the autopsy examinations, (2) the types of cases examined, (3) the location and etiology of the original infarction, (4) the thromboembolic phenomena found, (5) the hemorrhagic findings, (6) the frequency of ruptures, (7) the extent to which clinical diagnoses of various types were confirmed, and (8) miscellaneous conditions found inside and outside the heart. These various statistical findings are supplemented by Appendix F, Table 91 in which the major clinical findings, case by case, are compared with the major autopsy findings to facilitate the reader's awareness of typical errors and oversights in clinical diagnoses in myocardial infarction cases.

EXTENT OF AUTOPSY EXAMINATION

Frequency of Autopsy Examination

A total of 91 autopsies were performed on cases included in the series. These autopsies constituted 48 per cent of all the deaths that occurred in the present series and 9 per cent of the total series. Forty-seven of the autopsies were performed on cases included in the control group and 44, on cases in the treated group. The percentage of cases dying that were examined postmortem was about the same in the control and treated groups (49 and 47 per cent respectively), but the actual number for the treated group was lower because fewer treated group cases died.

Some slight rearrangement of the cases by treatment classification was necessary for the autopsy analysis since it was not feasible to correct the detailed autopsy observations for exceptions in treatment in the same manner as the major clinical counts. *Consequently, in all subsequent sections concerned with autopsy findings, cases are classified according to whether they actually did, or did not, receive anticoagulants rather than by whether they belonged in the control or treated*

Microscopic Reports

Microscopic reports were submitted for 83 per cent of the organs covered by gross reports. Of these microscopic reports, 72 per cent contained descriptions of the findings and the remaining 28 per cent, summaries only. Details by organs are given in Appendix F, Table 86. There was little difference between the cases receiving and not receiving anticoagulants with respect to the proportion of organs examined microscopically, the actual percentages being 84 and 82 per cent respectively However, a substantially higher proportion of the cases that had received anticoagulants were reported with a description, namely, 86 per cent, as compared with 61 per cent for those not receiving anticoagulants (see Appendix F, Table 87). One can presume that the inclusion of such descriptions was related in part to interest in the possibility of microscopic hemorrhages in cases receiving anticoagulants.

The extent of microscopic examination, organ by organ, is shown in Figure 163. It is probable that microscopic examinations were done with sufficient frequency for most purposes in the following organs: heart, lungs, liver, kidneys, spleen, pancreas and adrenals. There was, however, a sharp falling off in microscopic examinations of the gastrointestinal tract, *aorta* and *brain*, prostate, uterus, and testes. Leg vessels were so examined in one case, and arm vessels in none

COMPOSITION OF THE AUTOPSY SAMPLE

Certain general facts about the types of cases included in the autopsy sample are given in Table 155. Comparison of these data with corresponding counts for total deaths (see Appendix F, Tables 63, 64 and 68) indicates that little, if any, selection by age, sex, or severity at onset occurred in the process of determining which patients dying were examined at autopsy. The obvious differences between the composition of the autopsy sample and the total sample for the study result, therefore, from the types of cases that died in excessive numbers. For example, since more older than younger persons died, the average age of autopsy cases was 62.6 years as compared with the average age of 59.3 years for the total sample. Similarly, the age distribution of the autopsy sample was biased upward in comparison with the total sample, 63 instead of 45 per cent of autopsy cases being 60 years of age or over. Since a higher percentage of women than men died from their infarction, women constituted 29 per cent of the cases examined at autopsy, but only 23 per cent of the total sample. Likewise, since deaths were highest among those initially severely ill, 62 per cent of the autopsies were for patients severely ill at onset, while only 29 per cent of the total sample was reported as severely ill at onset. Selection of these types was to be expected. Confirmation of its occurrence should serve, however, as a warning that *autopsy findings cannot be presumed typical of all myocardial infarction cases.*

Since those saved from death by anticoagulant therapy cannot appear in an autopsy sample, the composition of the autopsy group was further affected by the differential effect of anticoagulants on survival. Since greater savings in lives were achieved with anticoagulant therapy among those mildly or moderately ill than among those severely ill (and also because a higher proportion of the treated group was initially severely ill), the group of cases receiving anticoagulants examined at autopsy was more heavily weighted with patients who were initially severely ill than was the control group (68 per cent as contrasted with only 56 per cent of those not treated with anticoagulants). On the other hand, since savings in lives with anticoagulants were greater at the older age levels, the average age of the cases treated with anticoagulants in the autopsy sample was lower than that for cases not receiving anticoagulants (aver-

frequent source of pulmonary emboli, it is quite obvious, on the basis of the experience in this study and many others, that this extremely significant portion of the vascular bed for the most part is being ignored in routine postmortem examinations. The even lower percentage of cases in which the vessels *of the arms were examined, namely, 2 per* cent, is not unexpected. If the generally accepted opinion that the veins of the arms are very rarely the site of spontaneous phlebothrombosis and consequently are not an important factor in the development of thromboembolic phenomena is correct, ignoring these vessels is of little consequence. Careful dissections might, however, fail to substantiate this contention.

In summary, then, one finds that at least two common sites of thromboembolic phenomena, namely, the brain and the vessels of the lower legs, were examined at postmortem in relatively few instances, so that thrombi or emboli in these areas were neither confirmed nor denied. This failure of pathologists to examine certain structures important in relation to intravascular clotting and its sequelae is apparently typical *and has been stressed repeatedly by those* interested in thromboembolic conditions, who rightfully contend that the bulk of autopsy statistics available in the medical literature fails to reflect accurately the total number of thromboembolic phenomena which are actually present in the autopsy material studied and reported. Since underreporting of this type clearly occurred in the present series, rates in the sections that follow are based wherever possible on the total number of organs examined rather than on the number of autopsies performed.

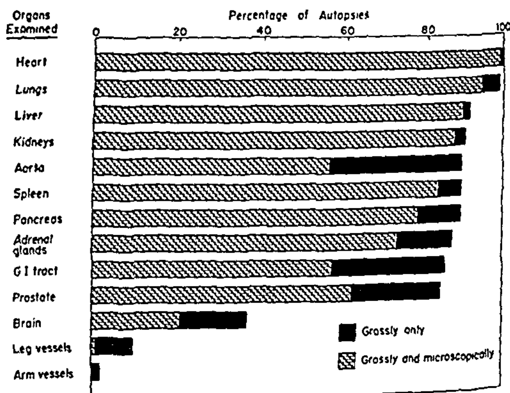


Figure 163. ORGANS EXAMINED AT AUTOPSY: Percentage of total autopsies in which various organs were examined both grossly and microscopically and percentage in which these organs were examined grossly only.

of anticoagulants through four days after the last dose). Even during this period, protection was in many cases inadequate, as previously demonstrated (see Chapter XII). About four days per case on the average were spent completely without protection and an additional 2.4 days were spent during the first three days when initial efforts to prolong the prothrombin time were being made. Coverage with anticoagulants was *particularly inadequate* for the 14 cases who received anticoagulants but died nevertheless during the first week. These cases received (exclusive of the first three days of therapy) only 1.2 days of anticoagulant therapy on the average, while an additional 13 treated cases dying during the second week received only 5.1 days of such therapy. Under these circumstances a full reflection in autopsy data of the possible effects of anticoagulant therapy cannot be expected.

In summary, therefore, it must be emphasized that (1) *many of the autopsy cases said to have received anticoagulants really received very little anticoagulant therapy of consequence*, and (2) *the patients who benefited most from anticoagulant therapy usually did not die and could not, therefore, be in the autopsy sample, while many of those cases that represent the actual and apparent treatment failures are included in the autopsy sample.* Consequently, the autopsy findings that follow would be expected to understate the advantages of anticoagulant therapy and overstate its hazards rather than the reverse. Several additional minor differences between the autopsy data for cases receiving and for cases not receiving anticoagulants also contribute further to this same understatement of the assets of anticoagulant therapy.

FINDINGS REGARDING THE ORIGINAL INFARCTION

The actual analysis of the autopsy data concerned in the first place the location and etiology of the original infarction. Since no

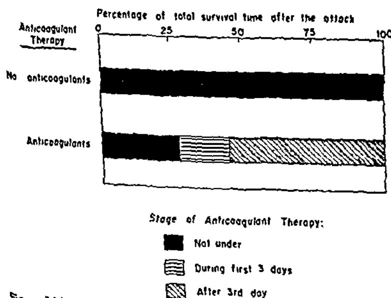


Figure 164. PROPORTION OF TIME UNDER ANTICOAGULANTS FOR AUTOPSY CASES. Percentage of total survival time after the attack that autopsied cases had been under anticoagulant therapy.

age ages were 61 and 64 years respectively). These are the major differences. They suggest selection in the direction of severity in the treated group, a fact that should again increase the difficulty of demonstrating the benefits of anticoagulants with autopsy data. Other minor differences between the control and treated groups appear in Table 155. In view of the relatively small numbers involved in these other differences, it is doubtful that they could have influenced in a significant manner the comparisons made later in this chapter.

The analysis of the effects of therapy as demonstrated at autopsy is handicapped further by the relatively short periods of time during which cases dying received anticoagulants. The cases in the autopsy sample who did not receive anticoagulants were observed a total of 613 days prior to their death, or an average of 12.8 days each. Cases receiving anticoagulants were observed a total of 564 days, or an average of 13.8 days each.* The proportion of their total illness during which they received anticoagulants is shown in Figure 164. It is evident at once that only a little more than half of the total time (7.5 days on the average) for those receiving treatment was spent under circumstances where dicumarol therapy, in the absence of supplementation, could, even under optimal circumstances, be adequate (i.e., the period from the 4th day

* This slightly longer period of observation increases the opportunity for the development of thromboembolic and hemorrhagic complications in the treated group and thus makes the demonstration of improvement slightly more difficult

TABLE 155

COMPOSITION OF THE AUTOPSY SAMPLE: Number and Percentage of Cases of Various Types among All Autopsy Cases and among Autopsy Cases Receiving and Not Receiving Anticoagulants

Age, Sex and Severity	All Autopsies		Autopsies of Cases Receiving No Anticoagulants		Autopsies of Cases Receiving Anticoagulants	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Age:						
Under 40	2	2	1	2	1	2
40–49	11	12	5	11	6	15
50–59	20	22	12	25	8	19
60–69	30	34	12	25	18	44
70–79	22	25	16	33	6	15
80–89	4	5	2	4	2	5
Average age	62.6	—	63.9	—	61.1	—
Sex:						
Males	63	71	36	75	27	66
Females	26	29	12	25	14	34
Severity at onset:						
Mild or moderate	34	38	21	44	13	32
Severe	55	62	27	56	28	68
Severity during course:						
Mild or moderate	10	11	5	10	5	12
Severe	79	89	43	90	36	88
Total autopsies*	89	100	48	100	41	100

* Excluding autopsy reports of two cases receiving anticoagulants in which the findings did not confirm the clinical diagnosis of a myocardial infarction

of anticoagulants through *four days* after the last dose). Even during this period, protection was in many cases inadequate, as previously demonstrated (see Chapter XII). About four days per case on the average were spent completely without protection and an additional 2.4 days were spent during the first three days when initial efforts to prolong the prothrombin time were being made. Coverage with anticoagulants was particularly inadequate for the 14 cases who received anticoagulants but died nevertheless during the first week. These cases received (exclusive of the first three days of therapy) only 1.2 days of anticoagulant therapy on the average, while an additional 13 treated cases dying during the second week received only 5.1 days of such therapy. *Under these circumstances a full reflection in autopsy data of the possible effects of anticoagulant therapy cannot be expected.*

In summary, therefore, it must be emphasized that (1) *many of the autopsy cases said to have received anticoagulants really received very little anticoagulant therapy of consequence*, and (2) *the patients who benefited most from anticoagulant therapy usually did not die and could not, therefore, be in the autopsy sample, while many of those cases that represent the actual and apparent treatment failures are included in the autopsy sample.* Consequently, the autopsy findings that follow would be expected to understate the advantages of anticoagulant therapy and overstate its hazards rather than the reverse. Several additional minor differences between the autopsy data for cases receiving and for cases not receiving anticoagulants also contribute further *to this same understatement of the* assets of anticoagulant therapy.

FINDINGS REGARDING THE ORIGINAL INFARCTION

The actual analysis of the autopsy data concerned in the first place the location and etiology of the original infarction. Since no

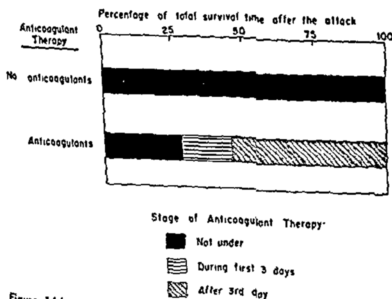


Figure 164. PROPORTION OF TIME UNDER ANTICOAGULANTS FOR AUTOPSY CASES: Percentage of total survival time after the attack that autopsied cases had been under anticoagulant therapy.

case was receiving anticoagulants at the time of the original occlusion, this infarction was uninfluenced by anticoagulant therapy. In consequence, the presentation focuses on the total group irrespective of treatment. The findings are of interest primarily for what they reveal regarding myocardial infarction as such and the accuracy of clinical diagnosis in the cases presented in this study.

Extent of Confirmation of the Original Diagnosis

Since inclusion in the sample was based in all cases on the clinical diagnosis only,[b] the autopsy findings provide a useful indication of the extent to which the clinical diagnoses were correct. A review of the protocols indicated that the presence of a recent myocardial infarction was confirmed in all but 2 of the 91 cases examined postmortem. For this component of the total sample, therefore, the basic diagnosis was correct in 98 per cent of the cases (see Figure 165). This relatively high record of diagnostic success was facilitated, no doubt, by the discarding from the sample of all cases in which the diagnosis appeared doubtful to the clinician. While this procedure undoubtedly led to the omission of some mild cases, it appears to have succeeded in assuring that the series was, in fact, a series of myocardial infarction cases.

In both the cases in which no recent myocardial infarction was found, there appeared to be some basis for the original error (see Appendix F, Table 91, case numbers 90 and 91). In one, severe coronary arteriosclerosis with focal calcification and stenosis and an old infarction were present and appeared to

[b] *Since the autopsy findings were available for only a small portion of the total sample, they could not be consistently utilized to define the selection of the sample.*

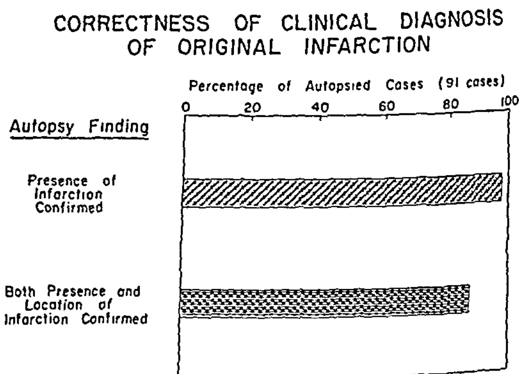


Figure 165. CORRECTNESS OF CLINICAL DIAGNOSIS OF ORIGINAL INFARCTION: Percentage of autopsied cases in which the clinical diagnosis of the original infarction was confirmed and percentage in which both the presence and the location of the original infarction as diagnosed clinically were confirmed at autopsy (based on total autopsied cases).

be the origin of the EKG findings that led to the diagnosis. In the other case, evidence of an old occlusion with an associated old infarction was found, but no evidence of the cause of death. Ventricular fibrillation was suspected. All further tables in this chapter omit these two cases in order that the discussion throughout may pertain only to cases exhibiting recent myocardial infarction. Both cases omitted had received anticoagulant therapy, but neither showed any unusual effects that, if included, would have altered the basic conclusions.

Etiology of the Original Infarction

The postmortem findings supported in general the accepted concept that myocardial infarction may occur as a result of any one of three types of coronary inadequacy: (1) coronary thrombosis, (2) coronary occlusion without thrombosis, or (3) coronary insufficiency without complete occlusion. Figure 166 gives a general picture of the findings regarding etiology and Table 156, the detailed counts.

Thrombi were by far the most important etiological factor, having produced 66, or 74 per cent, of the original infarctions. The group that had received no anticoagulants and those that had received such therapy were approximately comparable in this respect, the percentage of original infarctions due to thrombi in the two groups being 73 and 76 per cent respectively. Fifty-two of the original infarctions were due to a single new thrombus; 9, to multiple thrombi; 3, to thrombi *resulting* from the rupture of an atheromatous plaque; and 2, to thrombi secondary to a subintimal hemorrhage.

Another 8, or 9 per cent, of the infarctions were due to occlusions arising from causes other than thrombi. Three of these 8 were produced by arteriosclerotic plaques; 3, by advanced arteriosclerosis producing complete occlusion; 1, by the inward bulging of the wall of an artery due to a subintimal hemorrhage; and 1, by an occlusion of an unspecified type. Thirteen other infarctions (15 per cent) apparently arose from coronary insufficiency without a complete occlusion of the vessel concerned; at least no point of complete occlusion was discovered. Marked arteriosclerotic changes were the usual picture, combined in a few cases with an old occlusion or an old thrombus. The etiology of the infarctions in 2 instances (2 per cent) was unknown. Differences in the original etiology by treatment groups appear minor (Table 156 gives basic counts).

The importance of subintimal hemorrhage as a causative factor in coronary occlusion with myocardial infarction has been stressed by several workers, especially by Wartman[233, 234] and Paterson.[179, 180, 181] Generally confirmatory reports include those by Horn and Finkelstein[84] and by Nelson.[151] English and Willius,[53] however, while observing hemorrhagic lesions in the walls of coronary arteries in 54, or 40 per cent, of 135 hearts, directly or indirectly related to acute occlusions of the coronary artery in 20, concluded that "The intimal changes that coexisted with the hemorrhage appeared to represent the primary factor in the pathological condition; the hemorrhage was secondary. It does not seem logical, moreover, that hemorrhage in itself can have produced the effects observed."

On the other hand, French and Dock[67] found hemorrhage in the atherosclerotic plaques of the coronary arteries in only 5, or 6.3 per cent, of 80 soldiers with fatal coronary sclerosis, while Yater et al.[244] encountered hemorrhages in atherosclerotic plaques in only 12 per cent of subjects who died suddenly from coronary artery disease. Convincing data can be obtained only when serial cross-sections of the coronary arteries are studied, a practice not commonly observed. While attention was directed to this problem in this study, the protocols cannot be said to furnish conclusive evidence on this point.

While recognizing the inadequacy of the information available on this point in the

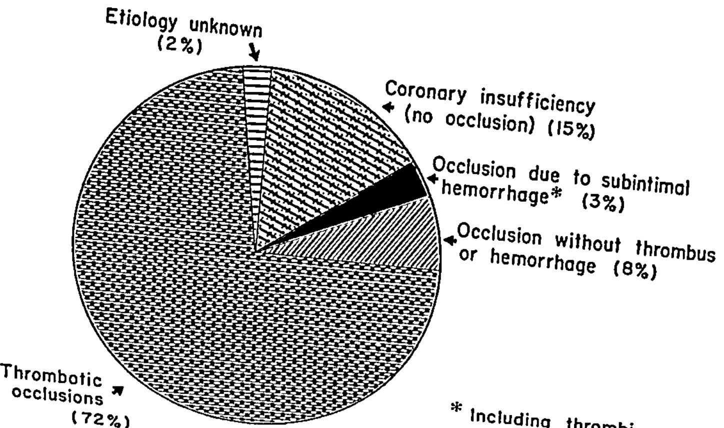


Figure 166. ETIOLOGY OF ORIGINAL MYOCARDIAL INFARCTIONS: Percentage of all original myocardial infarctions found at autopsy to have been due to various causes.

protocols submitted, the matter of subintimal hemorrhage was placed under special scrutiny in this analysis. Since microscopic reports on the heart were submitted on all but one of the 89 cases of myocardial infarction examined postmortem, a review of the prevalence of infarctions of this origin was possible within the limitations described. When all original infarctions in which a subintimal hemorrhage was found are counted regardless of whether a thrombus was, or was not, also present, only 3, or 3.4 per cent, of those examined microscopically could be said to be due to a subintimal hemorrhage.

TABLE 156

[illegible]

Etiology of Infarction	Original Myocardial Infarctions Found at Autopsy			
	Number			Per Cent of Total (89 Infarctions)
	Total	In Cases Receiving No Anticoagulants	In Cases Receiving Anticoagulants	
Coronary thrombi:				
Single new thrombus	52	26	26	58.6
New multiple thrombi	9	6	3	10.1
Thrombus secondary to subintimal hemorrhage	2[a]	2	—	2.2
Thrombus due to rupture of atheromatous plaque	3	1	2	3.4
Total due to thrombi	66	35	31	74.2
Other occlusion:				
Arteriosclerotic plaque producing occlusion	3	1	2	3.4
Subintimal hemorrhage producing inward bulging of wall of artery	1[a]	1	—	1.1
Advanced arteriosclerosis producing complete occlusion	3	2	1	3.4
Occlusion of unspecified type	1	—	1	1.1
Total due to other occlusion	8	4	4	9.0
Coronary insufficiency due to:				
Advanced arteriosclerosis	8	6	2	9.0
Old thrombus plus marked arteriosclerosis	2	1	1	2.2
Old occlusion plus marked arteriosclerosis	3	1	2	3.4
Total due to coronary insufficiency	13	8	5	14.6
Etiology unknown	2	1	1	2.2
All original infarctions	89	48	41	100.0

[a] Total in all categories due to subintimal hemorrhage is 3.4 per cent.

In two of these instances, the thrombus formation was associated with a subintimal hemorrhage, and in one additional case in which a *thrombus* was absent, the occlusion was produced by the inward bulging of a vessel wall over a subintimal hemorrhage. The descriptions of the 24 instances of secondary infarction subsequent to the original infarction (including extensions and new areas of infarction) in these same cases were also reviewed for evidence of subintimal hemorrhage. In no instance was such evidence reported, irrespective of the therapy received. *In this study, therefore, the postmortem reports fail to indicate that subintimal hemorrhage is often a factor in the production of myocardial infarction. If this is the case, the risk of anticoagulant therapy through augmentation of subintimal hemorrhage must be slight.* The effect of anticoagulants on infarctions originating from subintimal hemorrhage could not be tested in this series since only 3 cases were found at autopsy to have an original infarction due to subintimal hemorrhage and none of these had received any anticoagulants.

Location of the Original Infarction

As Figure 167 indicates, the most common site of the original infraction was the left ventricle. Nine in 10 of the original infra-

LOCATION OF ORIGINAL INFARCTION
(AUTOPSY CASES)

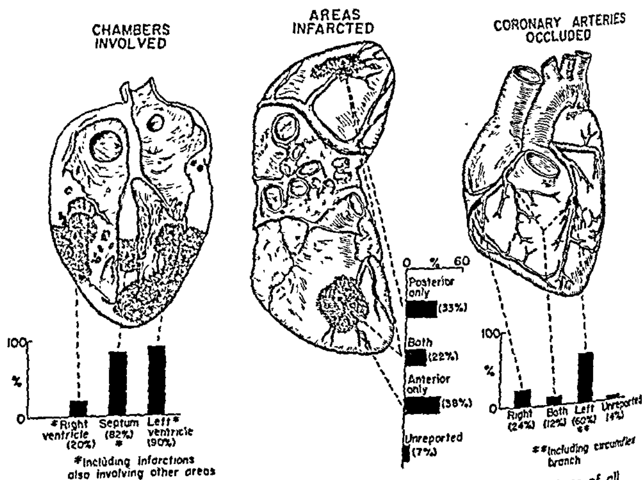


Figure 167. LOCATION OF ORIGINAL INFARCTION (AUTOPSY CASES): Percentage of all original myocardial infarctions found at autopsy that involved various chambers and areas of the heart and percentage resulting from the occlusion of various coronary arteries.

tions in the present series involved this area but 4 in 5 of those involving the left ventricle also involved the septum. The right ventricle was involved in only 2 autopsy cases in 10, and then usually in combination with the left ventricle and septum. Only one case showed an original infarction confined exclusively to the right ventricle. Sixteen protocols reported original infarctions extending to all three areas, the left and right ventricle and septum, while 7 involved the septum only.

Infarctions involving the left ventricle were somewhat more commonly anterior than posterior in location, but a fifth involved both areas. In contrast, infarctions involving the right ventricle were predominantly posterior in location, but a third were both anterior and posterior Involvement of the septum was common in both types but somewhat more frequent in anterior infarctions. When all infarctions are totalled regardless of the chamber involved, anterior infarctions exceed posterior infarctions (see Figure 167).

The most common site for the original occlusion was the left coronary artery, as Figure 167 again indicates In 53 protocols (60 per cent of the total) this was the only artery occluded. Thirty-seven protocols specified the anterior descending branch of this artery as the only site of the occlusion; 9, the circumflex branch; and 4, both branches. In the other 3 instances the occlusion probably occurred above the branches since no branch was mentioned in the protocol. An occlusion of the right coronary artery was found in 32 autopsied cases, but of these, 11, or about a third, also showed an occlusion of the left coronary artery. When the right coronary artery was occluded, usually no branch was specified. Only two reports mentioned the posterior descending branch and two, the circumflex branch.

Nearly all anterior infarctions resulted from the occlusion of the left coronary artery or one of its branches. The only exception noted was an instance in which an anomalous right coronary artery supplied the bulk of the myocardium with its blood supply. In contrast, posterior infarctions were more commonly the result of the occlusion of the right coronary artery or one of its branches, 7 in 10 of such infarctions being of this origin. The remainder involved the circumflex branch of the left coronary artery or occasionally, both arteries. No infarction confined to the posterior area and due to a single occlusion resulted from an occlusion of the anterior descending branch of the left coronary artery.

When the infarctions were tabulated by the chambers involved, infarctions of the left ventricle were found typically associated with occlusions of the left coronary artery rather than the right or its branches, the ratio being 3 to 1 when occlusions involving both arteries are omitted. Infarctions involving the septum followed a somewhat similar pattern as to the location of the occlusion (*i.e.*, 2.3 in the left to 1 in the right). Infarctions of the right ventricle, on the other hand, originated about equally from the occlusion of the right and left coronary arteries. Further details regarding the locations of the original infarctions and the chambers and arteries involved are given in Appendix F, Table 88.

These autopsy findings on the location of the original infarction were utilized further to evaluate the accuracy of the clinical diagnosis of the location of the original infarction. The results are summarized in Table 157 and Figure 165. Of the 83 cases for which both the clinical and the autopsy description of site were sufficiently clear to make possible this comparison, the findings in all but 4 cases were considered to confirm the electrocardiographic diagnosis. If judged from this base, therefore, the accuracy of the clinical (electrocardiographic) diagnosis of site in this series approximated 95 per cent. When measured against the total cases examined at autopsy (91 cases), the proportion in which both the presence and location of the infarc-

tion were clearly confirmed was 87 per cent (see Figure 165).

THROMBOEMBOLIC COMPLICATIONS FOUND AT AUTOPSY*

Since many thromboembolic complications are never recognized clinically, the evaluation of the consequences of anticoagulant therapy in the present study has been supplemented with a thorough consideration of the thrombi, emboli, and infarctions *found at autopsy*. The findings in these respects are reported in three following subsections which concern in sequence: (1) mural thrombi, (2) extensions and secondary infarctions of the myocardium, and (3) thromboembolic complications outside the heart.

* These and other selected findings based on the autopsy analysis were first presented orally by Dr I. S. Wright at the April, 1953 meeting of the American College of Physicians in Atlantic City

TABLE 157

AUTOPSY CONFIRMATION OF LOCATION OF ORIGINAL INFARCTION: Number of *Cases in Which the Location of the Original* Myocardial Infarction as Diagnosed Clinically was Confirmed or Not Confirmed at Autopsy

Location of Original Infarction as Diagnosed Clinically	Number of Autopsies in Which Clinical Diagnosis of Location Was Considered—	
	Confirmed	Not Confirmed
Anterior and anterolateral	33	2
Anteroseptal	13	—
Posterior and posterolateral	20	1
Posteroseptal	4	—
Anteroseptal and posteroseptal	1	—
Septal	3	—
Diffuse	2	1
Multiple infarctions initially	3	—
Total autopsies in which comparison of location was possible*	79*	4*

* To be included, a clear statement of location both clinically and at autopsy was required Consequently, these counts omit 4 cases in which the clinical description was not clear and 2 instances in which the autopsy description was not clear.

Intracardiac Thromboembolic Complications

Mural Thrombi

Mural thrombi occurring in association with myocardial infarction usually develop as a result of involvement of the endocardium by the infarction. Wartman and Hellerstein[349] reported that the intracardiac thrombi observed in 64 of the 160 cases of myocardial infarction studied by them were always directly beneath the infarction. Jordan et al.[170] found in 327 autopsied cases of myocardial infarction that in nearly all the hearts histological examination revealed evidence of infarction of the myocardium underlying the thrombi. However, mural thrombi may also form on areas of endocardium which are not infarcted, as in localized dilatations over infarcted myocardium and in the auricular appendages. They may be single or multiple and may occur in one or in more than one chamber of the heart. They are found most frequently, in association with myocardial infarction, in the left ventricle; less often, in the atria, and least often, in the right ventricle.

Mural thrombi are an exceedingly important source of emboli and yet are ordinarily recognized clinically only by inference from their consequences. Accurate evaluation of the effects of anticoagulant therapy on mural thrombi must rest, therefore, entirely on autopsy findings. These are reported in Tables 158 and 159 and in Figure 168 and are among the most important findings in the entire study. *About two-thirds (63 per cent) of the cases that had received no anticoagulants, but only a third (32 per cent), or about half as many, of the cases that had received any anticoagulant therapy showed mural thrombi at autopsy.* This marked difference occurred in spite of the very short periods of therapy received by many of the cases included in the treated group (pages 396–397). Even though the samples are small, this difference in the percentage of autopsy cases showing mural thrombi is

statistically significant. While the types of selection that determined the composition of the two autopsy samples can be appraised only roughly (see pages 395–397), there is no known selective factor that could explain such a marked difference.[d] It is therefore logical as well as medically reasonable to attribute the difference in the proportion of cases showing mural thrombi to anticoagulant therapy.

[d] Without the lower proportion of deaths due to hemorrhage or rupture in the control group, the contrast would be less but not absent. If deaths in which hemorrhage or rupture was a primary or contributing factor in death are artificially raised to the treated group level and all such cases are assumed to show *no* mural thrombi (an extreme assumption), the proportion of cases showing mural thrombi in the *control* group is lowered to 58 per cent—still a substantial contrast to the 32 per cent figure for treated cases even using this extreme assumption

TABLE 158

PREVALENCE OF MURAL THROMBI AT AUTOPSY: Number and Percentage of Cases in Which Mural Thrombi Were Found at Autopsy in One, Two, and Three Heart Chambers among Cases Receiving and Not Receiving Anticoagulants and Average Number of Chambers with Mural Thrombi per Case Examined at Autopsy

Number of Heart Chambers with Mural Thrombi Present	Cases Not Receiving Anticoagulants		Cases Receiving Anticoagulants	
	Number of Autopsies	Percentage of Autopsies	Number of Autopsies	Percentage of Autopsies
None	18	37.5	28	68.3
One chamber	22	45.8	11	26.8
Two chambers	6	12.5	2	4.9
Three chambers	2	4.2	—	—
Total with mural thrombi in any chamber	30	62.5	13	31.7
Total autopsies	48	100.0	41	100.0
Average number of heart chambers with mural thrombi per case examined	83	—	.37	—

A similar reduction in the occurrence of mural thrombosis under anticoagulants has been reported by Howell and Kyser.[154] These investigators found mural thrombi in 53 per cent of 98 autopsied myocardial infarction cases who had not received anticoagulants. On the other hand, only 29.5 per cent of 34 treated cases studied had mural thrombi. In patients with no mural thrombi, 5 probable embolic accidents were found, in patients with mural thrombi, 13.

The observation that untreated myocardial infarction cases show at autopsy a high incidence of mural thrombi has also been confirmed in other studies. Hellerstein and Martin[53] reported that in their series of 160 autopsied cases of myocardial infarction, 41 per cent showed mural thrombi. They have also listed the findings in regard to mural thrombi in seven other series in addition to their own, as follows:*

Authors	Number of Autopsies	Number of Cases With Mural Thrombi
Appelbaum and Nicolson	150	81
Bean	300	142
Levine and Brown	46	38
Lisa and Ring	100	31
Meakins and Eakin	62	29
Parkinson and Bedford	83	14
Wolff and White	23	7
This series (Hellerstein and Martin)	160	65
Total	924	410

Four of these series show rates above the 41 per cent reported by Hellerstein and Martin, the highest being 83 per cent reported by Levine and Brown. In general, in Hellerstein and Martin's series, peripheral occlusions were more frequent in cases with mural thrombi than in those without them

* Table reproduced from Am. Heart J. 33: 443 (Hellerstein and Martin[53]) with modifications.

tion were clearly confirmed was 87 per cent (see Figure 165).

THROMBOEMBOLIC COMPLICATIONS FOUND AT AUTOPSY*

Since many thromboembolic complications are never recognized clinically, the evaluation of the consequences of anticoagulant therapy in the present study has been supplemented with a thorough consideration of the thrombi, emboli, and infarctions found at autopsy. The findings in these respects are reported in three following subsections which concern in sequence: (1) mural thrombi, (2) extensions and secondary infarctions of the myocardium, and (3) thromboembolic complications outside the heart.

* These and other selected findings based on the autopsy analysis were first presented orally by Dr I. S. Wright at the April, 1953 meeting of the American College of Physicians in Atlantic City

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Anteroseptal and posteroseptal.	1	—
Septal	3	—
Diffuse	2	1
Multiple infarctions initially	3	—
Total autopsies in which comparison of location was possible*. . . .	79*	4*

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(55 per cent *vs.* 39 per cent), a fact that serves to emphasize the importance of mural thrombi.

Further examination of data for the present study as revealed in Figure 168 shows added details presumably also related to the therapy received. Thrombi were found in more than one chamber of the heart in 8 cases that had received no anticoagulants but in only 2 cases that had received such therapy. *On the average, cases that had received no anticoagulants showed mural thrombi in .8 heart chambers or appendages per case examined postmortem, whereas those who had received some anticoagulant therapy showed thrombi in only .4 chambers or appendages per case.* This difference was again statistically significant. One must conclude that either treated cases developed fewer mural thrombi, or that in treated cases these thrombi did not embolize and kill the patient. Probably both factors entered into the net result observed.

No count was attempted of the actual number of thrombi found since many protocols gave no actual count when clusters were present. It was possible, however, to tabulate the relation of the thrombus, or group of thrombi, to the infarcted area (see Table 159 and Figure 168). *Among cases that had received no anticoagulants, about a third of the mural thrombi or clusters of thrombi were located outside the infarcted area, while among those that had received some anticoagulant therapy, only one, or less than a tenth, occurred outside this area.*

Wartman and Hellerstein[110] found in their cases that the location of thrombi, by chambers, was as follows: left ventricle, 54; right auricle, 14; right ventricle, 4. There were mural thrombi in both auricle and ventricle in 8 cases. Yater et al.[111] reported the location of mural thrombi in their 43 cases with mural thrombi as follows: left ventricle, 37; right ventricle, 5; and in both ventricles, 2. They do not indicate that mural thrombi were found in the auricles. Jordan et al.[112] found in their autopsy series of 327 cases of myocardial infarction that the majority of intracardiac mural thrombi occurred in the left ventricle. Mural thrombi were found infrequently in the right ventricle and auricular mural thrombi, in only a small number of cases.

In this series, mural thrombi were also found most frequently in the left ventricle. This finding applies both to cases receiving and cases not receiving anticoagulants (see Table 159). About 86 per cent of the cases with mural thrombi showed thrombi in this chamber, a fact that is remarkably consistent with the previous finding that 90 per cent of the original infarctions involved this chamber. The right ventricle was involved in 20 per cent of the original infarctions and in about this same proportion of cases showing thrombi in any chamber. *The location of thrombi was thus approximately similar to that of the original infarctions.* Thrombi in the auricles or their appendages occurred exclusively in cases that had received no anticoagulants. The only thrombus that approached this area in a treated case was one case found to have a thrombus extending through a patent foramen ovale. In contrast, among cases that had received no anticoagulants, 5 showed a mural thrombus in the left auricular appendage; 2, a thrombus in the right auricle; and 2, a thrombus in the right auricular appendage.

Regardless of the method of analysis, therefore, the same conclusion is appropriate, namely, that *anticoagulant therapy was associated with a conspicuous and significant reduction in the prevalence of mural thrombi at autopsy.*

Extensions and New Myocardial Infarctions Found at Autopsy

The development of adequate statistical counts of intracardiac complications affecting the myocardium found at autopsy posed a problem statistically since it was often very difficult, if not impossible, to distinguish extensions of the original infarction from the original infarction itself. This

TABLE 159

LOCATION OF MURAL THROMBI AT AUTOPSY: Number of Autopsies in Which Mural Thrombi Were Found in Various Heart Chambers among Cases Receiving and Not Receiving Anticoagulants and Relation of Location of Mural Thrombi to Infarcted Areas

Chamber of Heart Involved[a]	Number of Cases with Mural Thrombi[b] in Given Chamber at Autopsy					
	Cases Not Receiving Anticoagulants (43 Cases)			Cases Receiving Anticoagulants (41 Cases)		
	Total[c]	Thrombus inside Infarcted Area	Thrombus outside Infarcted Area	Total[c]	Thrombus inside Infarcted Area	Thrombus outside Infarcted Area
Left ventricle	25	24	1	12	12	—
Right ventricle	6	4	2	2[d]	2	—
Left auricle	—	—	—	—	—	—
Left auricular appendage	5	—	5	—	—	—
Right auricle	2	—	2	—	—	—
Right auricular appendage	2	—	2	—	—	—
Through patent foramen ovale	—	—	—	1	—	1

[a] Cases with mural thrombi in more than one chamber are tabulated under each chamber involve

[b] Clusters of thrombi in the same chamber were tabulated as a single thrombus.

[c] Number is unduplicated since no heart chamber or appendage showed a mural thrombus both the infarcted area and outside such an area.

[d] One thrombus began in the right ventricle and grew into the right auricle and into the pulmona artery but was only one thrombus and is so counted.

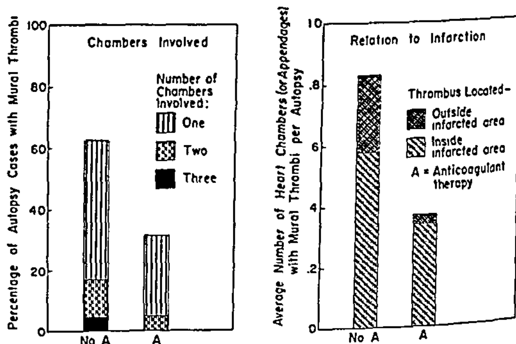


Figure 168. MURAL THROMBI: Percentage of autopsy cases with mural thrombi in one, two, and three heart chambers among cases receiving and not receiving anticoagulants and average number of heart chambers or appendages with mural thrombi per case receiving and not receiving anticoagulants, by relation of thrombus to infarcted area.

new thrombi (9 to a single new thrombus and 2, to multiple new thrombi). In 6 others for which no new thrombus was found, the extension of the infarction was presumed to have arisen as a result of an extension of the same thrombus that produced the original infarction, the new area of infarction being due to some enlargement, elongation, or shift in location of this original thrombus. Two other infarcted areas were traceable to arteriosclerotic plaques that produced occlusion associated with, or following, the original infarction. Four others resulted from coronary insufficiency. The etiology of the other infarction was not reported. If all infarctions due to thrombi (all but the last four categories) are assumed to be potentially preventable by anticoagulant therapy, a total of 17, or 71 per cent, of these extensions and secondary infarctions presumably might have been avoided had these patients been given anticoagulant therapy of optimal level and duration This proportion is almost exactly similar to the proportion of the original infarctions due to thrombi (72 per cent, excluding thrombi due to subintimal hemorrhage). *If these ratios are typical, it is unrealistic to expect that all secondary infarctions or extensions in the myocardium can be prevented by anticoagulant therapy, even under optimum conditions.* In this connection, it may be recalled (page 358) that in the present study three of the four "failures" of anticoagulant therapy to prevent thromboembolic complications under circumstances where adequate prothrombin levels had been maintained for three consecutive days were myocardial extensions and the fourth was a new myocardial infarction It is quite possible that some or all of these "failures" represented episodes that were not thromboembolic in character. However, since none of these "failures" came to autopsy, it was not possible to check this hypothesis against the facts.

The analysis of etiology also revealed a notable absence of secondary infarctions or extensions which, on the evidence submitted, could be ascribed to subintimal hemorrhage. *Although 41 cases received anticoagulants, no extension or new infarction of the myocardium was found due to subintimal hemorrhage or to a thrombus from such a hemorrhage. Thus, in this series, anticoagulants did not appear to increase this hazard.*

On the other hand, the present sample fails to demonstrate an improvement under anticoagulant therapy in the patients' prospects of escaping extensions and secondary infarctions in the myocardium. Thirteen extensions or new infarctions were found at autopsy among cases who had not received anticoagulants (27 per 100) and eleven (also 27 per 100) among cases that had received some anticoagulant therapy (see Table 160 and Figure 169). If counts are limited to potentially preventable episodes, namely, those due to thrombi, the division still remains about equal, namely 9 and 8 in the untreated and treated groups respectively. The averages on this revised basis (namely, 18 8 and 19.5 per hundred cases among cases not receiving anticoagulants and receiving anticoagulants respectively) still show no difference of consequence.

It cannot be concluded, however, that anticoagulants are of no benefit with respect to intracardiac thromboembolic complications since other explanations of this lack of difference seem reasonable. It may be due, for example, to the selected nature of the autopsy sample Since extensions or secondary infarctions often are the immediate cause of death in myocardial infarction cases, cases selected by reason of the fact that they died may not give the correct picture in regard to the potentialities of anticoagulants in preventing intracardiac complications. That selection of this type actually occurred is suggested by the fact that the autopsy group (selected by reason of death) showed little difference of consequence in the average number of intracardiac complications *diagnosed clinically*, the averages being 21 and 17 per hundred cases in the

difficulty was especially acute when the second clinical thromboembolic episode occurred shortly after the original incident, since in such cases the age of the extension was anatomically indistinguishable from that of the original infarction. In 4 instances in which an extension had been diagnosed clinically, the size of the area involved and the freshness of the infarction found at autopsy were compatible with an extension, but the area involved could not be distinguished from that of the original infarction. Since separate episodes had been distinguished clinically, these diagnoses were counted as confirmed at autopsy in spite of this difficulty. Two other instances in which the autopsy evidence was not considered to confirm the prior clinical diagnosis of an extension are omitted from the counts of autopsy findings that follow (see page 411). It is possible that other extensions that were not observed clinically are similarly omitted from the autopsy counts because they were indistinguishable at autopsy from the original infarction. To the extent to which such omissions occurred, the counts of secondary episodes cited are understatements.

A summary of autopsy findings with respect to thromboembolic complications in the myocardium is given in Table 160 and Figure 169. As defined above, a total of 20 extensions and 4 new infarctions were observed at autopsy. In other words, about one case in four in the present series that came to autopsy showed one or more secondary infarctions in the myocardium. Slightly less than half of these could clearly be traced to

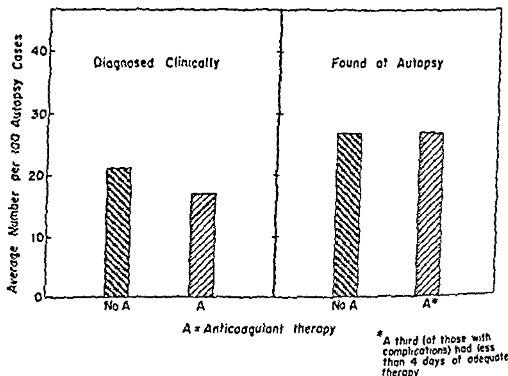


Figure 169. EXTENSIONS AND SECONDARY MYOCARDIAL INFARCTIONS AT AUTOPSY: Average number of extensions and secondary myocardial infarctions diagnosed clinically and average number found at autopsy per hundred autopsy cases receiving and not receiving anticoagulants.

new thrombi (9 to a single new thrombus and 2, to multiple new thrombi). In 6 others for which no new thrombus was found, the extension of the infarction was presumed to have arisen as a result of an extension of the same thrombus that produced the original infarction, the new area of infarction being due to some enlargement, elongation, or shift in location of this original thrombus. Two other infarcted areas were traceable to arteriosclerotic plaques that produced occlusion associated with, or following, the original infarction Four others resulted from coronary insufficiency. The etiology of the other infarction was not reported. If all infarctions due to thrombi (all but the last four categories) are assumed to be potentially preventable by anticoagulant therapy, a total of 17, or 71 per cent, of these extensions and secondary infarctions presumably might have been avoided had these patients been given anticoagulant therapy of optimal level and duration. This proportion is almost exactly similar to the proportion of the original infarctions due to thrombi (72 per cent, excluding thrombi due to subintimal hemorrhage). *If these ratios are typical, it is unrealistic to expect that all secondary infarctions or extensions in the myocardium can be prevented by anticoagulant therapy, even under optimum conditions.* In this connection, it may be recalled (page 358) that in the present study three of the four "failures" of anticoagulant therapy to prevent thromboembolic complications under circumstances where adequate prothrombin levels had been maintained for three consecutive days were myocardial extensions and the fourth was a new myocardial infarction. It is quite possible that some or all of these "failures" represented episodes that were not thromboembolic in character However, since none of these "failures" came to autopsy, it was not possible to check this hypothesis against the facts.

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untreated and treated groups respectively, a difference that is not statistically significant. This small and insignificant difference is in marked contrast to the substantial and statistically highly significant differences in rates for clinically diagnosed intracardiac complications for the *total* control and treated groups, namely, 15.8 per hundred cases in the control group and 5.1 per hundred cases in the treated group. Many of the cases saved from intracardiac complications by anticoagulant therapy obviously do not appear in the autopsy sample and hence cannot affect the comparison. To this explanation in terms of selection may be added two others, namely, the small amount of anticoagulant therapy received by some of the treated autopsy cases,[f] especially those who died during the first week, and chance factors that can render observations on small samples surprisingly variable. This interpretation of the lack of differences in terms of factors irrelevant to the protective power of anticoagulants is further supported by the previously reported low records for mural thrombi and clinically diagnosed intracardiac complications found associated with anticoagulant therapy. *Therefore, the absence of significant differences in extensions and secondary myocardial infarctions found at autopsy between those who had received and not received anticoagulants should not be considered grounds for withholding anticoagulant therapy.*

With a different approach, the autopsy findings with reference to the myocardium also can be used to throw light on a secondary question of interest, namely: What are the chances of diagnosing extensions and new secondary infarctions clinically? *Comparison of the autopsy findings with the clinical diagnoses* (see Table 160 for complication counts; Appendix F Table 91 for individual case comparisons; and Figure 170 for case counts) *indicated that fifteen, or about two-thirds, of the complications of these*

TABLE 160

EXTENSIONS AND SECONDARY MYOCARDIAL INFARCTIONS AT AUTOPSY: Total Number of Extensions and Secondary Myocardial Infarctions Found at Autopsy among Cases Receiving and Not Receiving Anticoagulants, Correctness of the Diagnosis of Such Complications Clinically, and Average Number Found at Autopsy and Diagnosed Clinically per Hundred Autopsies

Relation of Clinical and Autopsy Diagnosis	Cases Not Receiving Anticoagulants (45 Autopsies)	Cases Receiving Anticoagulants (41 Autopsies)
	Number Reported[a]	
Extensions and secondary myocardial infarctions:		
Found at autopsy:		
Diagnosed clinically.	8	7
Not diagnosed clinically	5	4
Total found at autopsy	13	11
Diagnosed clinically:		
Confirmed at autopsy[b]	8	7
Not confirmed at autopsy	2	—
Total diagnosed clinically....	10	7
Net clinical error .	−3	−4
	Average Number per 100 Cases[a]	
Total found at autopsy..	27	27
Total diagnosed clinically.	21	17

[a] Case counts may be secured from the data in this table by subtracting 1 from both 8's (line 1 and line 4 in this table) since only one case showed more than one extension and no case showed more than one secondary infarction. This case received no anticoagulants and developed two extensions, both of which were diagnosed clinically and confirmed at autopsy.

[b] This line repeats line 1 of this table.

[f] A third of the cases receiving anticoagulants and showing extensions or secondary myocardial infarctions or mural thrombi in the heart chambers at autopsy had had less than 4 days of anticoagulant therapy. For the other two-thirds, nearly half of the known prothrombin readings after the first day of anticoagulant therapy were below the lower limit of the therapeutic range (25 seconds, converted).

types had been diagnosed clinically—a considerably better record for clinical diagnostic accuracy than was achieved for extracardiac thromboembolic complications, as will be later demonstrated. Perhaps indicative of the source of such errors as occurred is the fact that all nine misses were extensions rather than new infarctions. Because extensions by definition occur in the same area as the original infarction, new episodes are particularly difficult to distinguish from the developmental pattern of the original infarction, especially when they occur close together in time.

The reverse type of error, namely, the clinical diagnosis of extensions or new secondary infarctions where none was evident at autopsy, occurred in only two instances. In one, a progression noted on an EKG record taken one week after the initial attack but six days before death was diagnosed as an extension. At autopsy, two occlusions produced by two thrombi were found, one in the anterior descending branch of the left coronary artery and the other, in the right marginal. However, since neither an area of extension of the infarction nor a new area of infarction was distinguishable at autopsy from the original infarction, the clinical diagnosis of a second episode was conservatively appraised as not confirmed. Apparently, however, an early second occlusion actually occurred, but had been confused clinically with an extension, a point of relatively minor importance. In the second case, the patient had undergone an acute episode of severe pain which clinically seemed like an extension and was accompanied by a marked drop in blood pressure, but not by EKG changes. At autopsy, the episode was found to have been a rupture of the interventricular septum. Thus in both instances a definite additional change in the pathological picture had been recognized but incorrectly analyzed.

Since for the autopsy sample a total of nine episodes were missed clinically and only two probably nonexistent were diagnosed

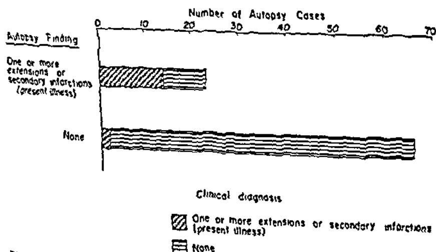


Figure 170. CORRECTNESS OF CLINICAL DIAGNOSIS OF EXTENSIONS AND SECONDARY MYOCARDIAL INFARCTIONS: Number of autopsy cases in which one or more extensions or secondary myocardial infarctions were or were not found at autopsy, by relation of autopsy finding to clinical diagnosis.

in excess, the net error in the clinical counts for extensions and secondary infarctions was clearly in the direction of understatement. *If this sampling is representative, the general clinical counts of intracardiac thromboembolic complications previously reported* (see Chapter VIII) *also understate the frequency of such episodes and hence the urgency of the need for anticoagulant therapy.* Presumably, however, diagnostic errors of these types were unassociated with treatment* and hence presumably would balance out without affecting the evaluation of the consequences of anticoagulants for thromboembolic complications in the myocardium in comparisons made with a control group observed under similar conditions by the same physician.

In addition to an understatement of frequency, a less important type of error occurred in 3 instances, namely, an erroneous classification of the type of episode. In two instances, episodes diagnosed clinically as new infarctions were found at autopsy to be extensions and in one other, an episode diagnosed clinically as an extension was found at autopsy to be a new infarction. This type of distinction is minor and does not affect the accuracy of the basic conclusions with respect to therapy since in most instances the two types have been presented together in composite totals.

Extracardiac Thromboembolic Complications

Frequency of Observation at Autopsy

Extracardiac thromboembolic complications were an exceedingly common autopsy finding. In the present series they were more than three times as numerous as extensions and new infarctions in the myocardium for the same group. The lungs were the most frequent site of extracardiac complications and the kidneys, the next most common location. It is noteworthy that these organs also ranked first and second respectively in the series of Hellerstein and Martin,[13] Bean,[14] Garvin,[72] and Meakins and Eakin,[104] hence they may be assumed to be the organs of maximum risk. The other areas in the present series in which such complications were found, listed in descending order of frequency per organ examined, were: aorta, brain, spleen, liver, and adrenal glands. The ranking of the legs as a site of thrombi is undetermined since the leg veins were examined in only 9 cases, but the fact that two of these nine cases showed thrombi serves to re-emphasize the well-known fact that the legs are also a common site for thromboembolic phenomena.

Because of the difficulty in finding and identifying the thrombi or emboli, these counts include infarctions both with and without obvious thrombi or emboli as well as thrombi without infarctions. They exclude, however, those infarctions and thrombi judged on the basis of autopsy evidence of age to antedate the present illness. Infarctions due to hyperplasia were also excluded.

By this definition, a total of 78 extracardiac thromboembolic complications were found at autopsy. About 2 in 5 of these were infarctions and 3 in 5, thrombi without infarction. For 9 of the lung infarctions, an accompanying embolus was found and for 4 of the kidney infarctions, an accompanying thrombus. No emboli or thrombi were reported observed in association with the other infarctions. The thrombi without accompanying infarction were distributed by organs as follows: 15 in the aorta (mostly mural thrombi), 4 in the right popliteal veins, 3 in the pelvic veins (all involving one

* Misses found at autopsy were equally frequent in the two groups. Five cases with extensions, or 10 per cent, of the total cases were missed in the group receiving no anticoagulants and 4 cases (10 per cent), in the group that had received antico-

the heart (see Table 100).

TABLE 161

INFARCTIONS AND THROMBI OUTSIDE THE HEART AT AUTOPSY: Total Number of Infarctions with and without Emboli or Thrombi and Total Number of Thrombi without Infarctions Found outside the Heart at Autopsy among Cases Receiving and Not Receiving Anticoagulants

Autopsy Finding	Number of Given Type Found Outside the Heart at Autopsy		
	All Cases	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants
Infarctions[a]:			
Embolus found	9	9	—
Thrombus found	4	4	—
Neither embolus nor thrombus found	20	12	8
Total infarctions	33	25	8
Thrombus without accompanying infarction[b]	45	35	10
Total extracardiac thromboembolic complications found at autopsy	78	60	18
Total autopsies in which any area outside the heart was examined	88	48	40

[a] Multiple infarctions in the same lung or kidney were counted only as single complications unless more than one episode involving this site had been diagnosed clinically, or the autopsy evidence indicated that the infarctions were clearly of differing age, since it was believed they might have originated from the fragmentation of a single embolus. One infarction in the prostate was omitted because it was reported to be due to hyperplasia and not to an embolus or thrombus.

[b] For computation purposes, cases reported as showing "multiple" thrombi in a given artery or area but with no exact count reported were estimated to have three thrombi, this being considered a minimum estimate of the number of separate developments. One free clot in the vena cava was not counted as a thrombus since it was not certain that it originated antemortem.

patient), and 1 each in the iliac, perivesicular, uterine, bladder, right renal, right ovarian, cystic, left subclavian, left common iliac, and adrenal veins. Six of these thrombi were found in a single patient—one who had received no anticoagulant therapy (see case number 62, Appendix F Table 91). Details for total counts by treatment groups, as well as the counting procedures used, are specified in Table 161.

The contrast between patients who had received anticoagulant therapy and those who had not (shown in Table 162 and in Figure 171) is striking. Twenty-one, or 44 per cent, of the cases who had received no anticoagulants showed one or more such complications at autopsy as contrasted with only 11, or 28 per cent, of the cases that had received some anticoagulant protection.[a] This figure of 44 per cent for untreated cases corresponds almost exactly with Hellerstein and Martin's report[15] that 45 per cent of the 160 autopsy myocardial infarction cases they analyzed showed emboli or thrombi outside the heart at autopsy. These complications were a major or contributing cause of death in 59 per cent of the cases in their series showing such complications. In contrast, only 15 per cent of autopsy cases of similar age dying from causes other than myocardial infarction showed any thrombi or emboli, fatal or otherwise.

Examination of the extent of the anticoagulant therapy received by the 11 treated cases showing extracardiac thromboembolic complications at autopsy revealed that 6 of the 11 had received less than 4 days of anticoagulant therapy. The remaining 5 showed prothrombin readings below 25 seconds (converted) for more than half of all their days of anticoagulant therapy with known readings between the second day of this therapy and the day of their last dose, inclusive. This low level of anticoagulant protection was, no doubt, responsible for

[a] See footnote j, p 415

TABLE 162

CASES WITH EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS AT AUTOPSY:
Number and Percentage of Cases with One or More Thromboembolic Complications outside the Heart Diagnosed Clinically and Found at Autopsy among Autopsy Cases Receiving and Not Receiving Anticoagulants

Status of Anticoagulant Therapy	Number of Cases In Which Any Area outside the Heart Was Examined[a]	Cases with Extracardiac Thromboembolic Complications			
		Diagnosed Clinically[b]		Found at Autopsy	
		Number of Cases	Percentage of Cases	Number of Cases	Percentage of Cases
Cases receiving no anticoagulants.....	48	8	17	21	44
Cases receiving anticoagulants........	40	4	10	11	28

[a] For number of specific organs examined, see Table 165.
[b] Includes cases in which thromboembolic complications outside the heart were diagnosed clinically in specific areas not examined at autopsy.

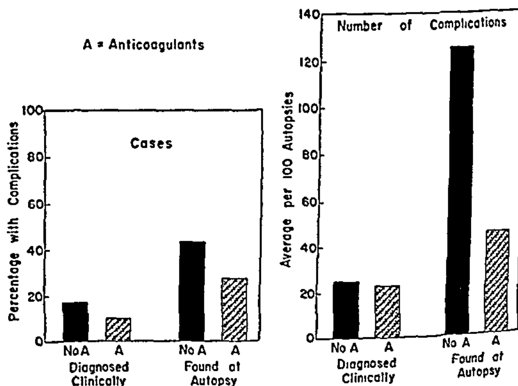


Figure 171. EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS AT AUTOPSY: Percentage of autopsy cases in which extracardiac thromboembolic complications were found, average number of such complications per hundred autopsies, and corresponding rates for complications diagnosed clinically among autopsy cases receiving and not receiving anticoagulants (rates for number of complications adjusted to equalize number and type of organs examined in each group).

some of the thromboembolic phenomena found in these treated cases.

Contrasts stated in terms of the number of extracardiac thromboembolic complications found were greater than those for case counts (see Table 163). The untreated cases showed a total of 60 thromboembolic complications and the treated, 18 complications. When converted to a comparable base (i.e., number per hundred cases), *the averages became 125 for those who had received no anticoagulants and only 45 for those who had received some anticoagulant therapy.*[i] The average for the treated cases was thus only about a third as high as that for the untreated cases.[j] A difference of this amount and in this direction would occur less than twice in one hundred times on a chance basis.[k] *Anticoagulant therapy was obviously associated with a substantial reduction in the number of extracardiac thromboembolic complications found at autopsy.*

A further contrast in the experience of the two groups becomes apparent in Table 164. Only 2 cases that had received anticoagulants showed three or more extracardiac complications and none, more than four.

TABLE 163

CORRECTNESS OF CLINICAL DIAGNOSIS OF EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS. Total Number of Extracardiac Thromboembolic Complications Found at Autopsy among Cases Receiving and Not Receiving Anticoagulants, Correctness of the [illegible]

Relation of Clinical and Autopsy Diagnosis	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants
	Number Reported	
Extracardiac thromboembolic complications:		
Found at autopsy:		
Diagnosed clinically	8	2
Not diagnosed clinically	52	16
Total found at autopsy	60	18
Diagnosed clinically		
Confirmed at autopsy[a]	8	2
Not confirmed; organ concerned—		
Examined	2	3
Not examined	2	4
Total diagnosed clinically	12	9
Net clinical error[b]	−50	−13
	Average Number per 100 Cases[c]	
Total found at autopsy	125	45
Total diagnosed clinically	25	23
Total autopsies in which any area outside the heart was examined	48	40

[a] This line repeats line 1 of this table

[b] Omitting diagnoses for organs not examined

[c] Based on total cases with any area outside the heart examined

[i] While the organs examined in the two groups are not exactly comparable (see Appendix F Table 86), there is no reason to believe that the difference results from this factor, since similar differences were found organ by organ (see Table 165). Statistical correction for this lack of perfect comparability is not feasible since the number of other arteries and veins examined in the two groups is unknown.

[j] This contrast is somewhat augmented by the lower proportion of the untreated autopsy cases in which hemorrhage or rupture contributed to death However, the effect of this factor is minor as can be demonstrated by arbitrarily adding to the untreated group a sufficient number of deaths due to rupture or hemorrhage to equalize this factor and assuming that none of these added cases had any extracardiac thromboembolic complications—an extreme assumption. On this basis the percentage of untreated autopsy cases showing extracardiac complications becomes 41 instead of 44 per cent and the average number of such complications per case, 1 17 instead of 1.25. Thus substantial contrasts remain in spite of the extreme underlying assumption involved.

[k] Contrary to most significance statements in the text, this statement is based on a one-tailed test Since there is no reason to believe that anticoagulants would increase thromboembolism, the use of the one-direction test appears justified in this instance

TABLE 162

CASES WITH EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS AT AUTOPSY: Number and Percentage of Cases with One or More Thromboembolic Complications outside the Heart Diagnosed Clinically and Found at Autopsy among Autopsy Cases Receiving and Not Receiving Anticoagulants

Status of Anticoagulant Therapy	Number of Cases in Which Any Area outside the Heart Was Examined[a]	Cases with Extracardiac Thromboembolic Complications			
		Diagnosed Clinically[b]		Found at Autopsy	
		Number of Cases	Percentage of Cases	Number of Cases	Percentage of Cases
Cases receiving no anticoagulants.....	48	8	17	21	44
Cases receiving anticoagulants........	40	4	10	11	28

[a] For number of specific organs examined, see Table 165.

[b] Includes cases in which thromboembolic complications outside the heart were diagnosed clinically in specific areas not examined at autopsy.

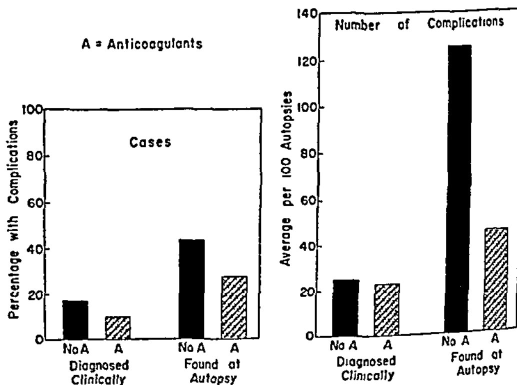


Figure 171. EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS AT AUTOPSY: Percentage of autopsy cases in which extracardiac thromboembolic complications were found, average number of such complications per hundred autopsies, and corresponding rates for complications diagnosed clinically among autopsy cases receiving and not receiving anticoagulants (rates for number of complications adjusted to equalize number and type of organs examined in each group).

ose cases with whom anticoagulants were s effective, or those treated inadequately, d a much greater chance of being in the *itopsy sample* by reason of death than did ose with whom anticoagulants were emloyed more adequately or with greater ffectiveness In spite of this marked selecion, however, these very dramatic contrasts *revealed.*

Correctness of Clinical Diagnosis of Extracardiac Thromboembolic Complications

Another notable finding of the autopsy analysis was the very large number of thromboembolic complications never diagnosed or even suspected clinically. Even though the autopsy examinations were often incomplete, a total of 68 thromboembolic complications were found outside the heart at autopsy that had never been diagnosed clinically. The statistical details are given in Table 163, Appendix F Table 89, and Figure 173 and the details case by case, in Appendix F, Table 91. Together these data constitute clear and dramatic evidence of how inadequately *thromboembolic complications* in acute coronary occlusion with myocardial infarction are recognized clinically, even in teaching hospitals equipped with all of the most modern and elaborate of diagnostic aids. They also help to explain why many clinicians, especially those who do not obtain autopsies routinely, state they encounter very few thromboembolic complications in their cases of myocardial infarction.

TABLE 165

LOCATION OF EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS AT AUTOPSY:

Percentage of Cases with Thromboembolic Complications Found in Various Locations outside the Heart at Autopsy among Cases Receiving and Not Receiving Anticoagulants and Number of Such Complications per Hundred Autopsy Cases

Location	Number of Autopsies in Which Organ Was Examined		Extracardiac Thromboembolic Complications Found at Autopsy			
			Percentage of Cases with Complications		Average Number per 100 Cases	
	Cases Not Receiving Anticoagulants	Cases Receiving Anticoagulants	Cases Not Receiving Anticoagulants	Cases Receiving Anticoagulants	Cases Not Receiving Anticoagulants	Cases Receiving Anticoagulants
Lungs	48	40	23	8	38	10
Kidneys	45	35	18	6	31	6
Brain	22	11	*5*	*9*	*5*	*9*
Spleen	45	34	2	6	2	6
Adrenal glands	45	32	0	3	0	3
Liver	45	36	2	0	2	0
Aorta	41	38	12	5	27	11
Leg veins	4	5	—[a]	—[b]	—[a]	—[b]
Other veins	—[a]	—[a]	—[b]	—[d]	—[d]	—[d]

Note: *Italics are used when percentages and ratios quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] Two cases in the group receiving no anticoagulants showed [illegible]

[illegible] complications were found in other veins in 4 cases not receiving anticoagulants and 4 complications, in other veins in 2 cases receiving anticoagulants but no ratios are quoted since the number of cases with other veins examined is unknown

Of the untreated cases, however, 10 showed 3 or more thromboembolic complications and 3 showed 6 or more, the highest number in any single case being 8. These counts, moreover, are conservative since (1) multiple infarctions within the same lung or kidney were counted as one complication only, regardless of the number of separate new infarcted areas found, unless separate episodes had been distinguished clinically or the ages of the various infarctions were distinguishable at autopsy, and (2) multiple thrombi, even though reported as "numerous," were estimated for these counts to equal a maximum of 3 in any given organ. This procedure had the effect of reducing the counts for the untreated group considerably more than those for the treated group since both multiple infarctions and multiple thrombi in the same organ were more numerous among untreated than treated cases.[1]

Contrasts between treatment groups were most spectacular for the kidneys where complications averaged 31 per hundred among untreated cases and only 6 per hundred among treated cases (see Table 165 and Figure 172). The lungs ranked next in degree of contrast with 38 complications per 100 cases in the untreated group and 10 per 100 in the treated group. In the aorta, those not receiving anticoagulants showed 27 thrombi per 100 cases as contrasted with only 11 per 100 cases among those who had received anticoagulants. Of the 5 treated cases with leg veins examined, none showed thrombi, but 2 of the 4 untreated cases with leg veins examined showed thrombi, one of these cases having multiple thrombi in the popliteal veins. Full details by organs are given in Table 165 and Appendix F, Table 89

These contrasts associated with anticoagulant therapy are the more notable since Table 163 and Figure 171 indicate further the presence of selection in the autopsy group that would affect adversely the treated group findings. It will be noted, for example, that the treated group studied *at autopsy* showed *clinically* an average number of complications that was nearly equal to (i.e., 90 per cent of) that of the corresponding average for the untreated group, whereas it was previously shown in Chapter VIII that the total treated group average was only about three-tenths that for the total control group. The explanation is obviously that

TABLE 164

SINGLE AND MULTIPLE EXTRACARDIAC [illegible]

Case Receiving and Not Receiving Anticoagulants and Average Number of Such Complications per Case

Number of Extracardiac Complications* Found at Autopsy per Case Examined Postmortem	Number of Cases	
	Cases Not Receiving Anticoagulants	Cases Receiving Anticoagulants
None	27	29
One	10	7
Two	1	2
Three	3	1
Four	2	1
Five	2	—
Six	1	—
Seven	1	—
Eight	1	—
Total autopsy cases with any area outside the heart examined	48	40
Average number per case	1.25	.45

* For explanation of counting procedures, see footnotes a and b of Table 161.

[1] For example, the counts for infarctions were reduced by this procedure for 6 cases that had received no anticoagulants but for only 1 case that had received anticoagulants. Also, there were 8 instances of multiple thrombi in the same organ among cases not receiving anticoagulants, but only 2 instances among cases receiving anticoagulants. If each organ with multiple thrombi had been counted as having only one thrombus, the average number of complications per hundred cases would have been 92 for those not receiving anticoagulants and 35 for those receiving anticoagulants. The percentage reduction is altered by only 2 percentile points by this procedure.

nomena. In one case, symptoms believed clinically to represent a pulmonary infarction were found at autopsy to be due to confluent lobular pneumonia. In a second case, the patient developed hemiplegia clinically which, on neurological examination, was attributed to a cerebral embolus. At autopsy, no hemorrhage, embolus, or thrombus was found and no other explanation for the hemiplegia was apparent. Possibly some small embolus or thrombus was present in the brain but was missed at autopsy. The other three instances of overdiagnosis clinically were all diagnoses of lung emboli, all three occurring in the same case. The first of these lung infarctions was reported to have occurred prior to hospitalization, diagnosis having been based on a history of chest pain, plus the local physician's finding of lung disease. The second diagnosis of a lung infarction in this patient was based on the developement, concurrently with phlebothrombosis of the leg, of a pleural friction rub and chest pain that became worse on respiration. The third diagnosis, that of a massive pulmonary infarction, was a presumptive one, postulated as an explanation for a sudden death. At autopsy, no lung infarction was found and no other explanation for the symptoms that led to these three diagnoses was apparent, with the possible exception of the finding that an extension of the original myocardial infarction had occurred.

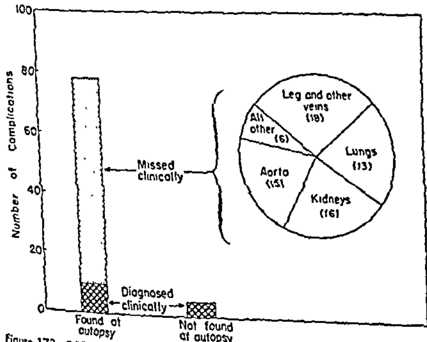


Figure 173. CORRECTNESS OF CLINICAL DIAGNOSIS OF EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS. Total number of thromboembolic complications found outside the heart at autopsy which had or had not been diagnosed clinically, number in specific organs missed clinically and number in organs examined at autopsy diagnosed clinically and not found at autopsy.

The clinical diagnosis of extracardiac complications was considerably less successful than was that of extensions and secondary infarctions of the myocardium. While only about 1 in 3 such complications in the myocardium were missed clinically, about 7 in 8 extracardiac complications were missed. Of these, 16 were in the kidneys, 15 in the aorta, 13 in the lungs, 18 in the legs or other veins, 3 in the spleen, and 1 each in the adrenal glands, brain, and liver. In most cases, no clinical symptoms that would suggest such complications were reported. Only careful and painstaking routine autopsy studies of cases dying can reveal the full extent of these complications. Since under current practice, the vessels of the legs are not usually examined postmortem, even these figures understate the full extent of venous thromboses in the lower extremities. This is regrettable since the legs are an extremely important site of thromboses and the source of many of the most serious pulmonary emboli.

As Figure 173 indicates, underdiagnosis was the typical clinical error. Of the 78 thromboembolic complications found at autopsy, only 10, or slightly more than a tenth, had been diagnosed clinically. Six others, all in the arms or legs, had been diagnosed clinically but could not be either confirmed or disproved at autopsy since the vessels concerned were not examined. In addition, 5 instances of possible overdiagnosis occurred (i e., complications diagnosed clinically but not confirmed at autopsy even though the organ was examined). Two of these instances occurred in cases that had not received anticoagulants and 3, in cases that had received anticoagulants—an approximately equal division. Thus for this autopsy sample no disproportionate number of excess diagnoses appears to have been made clinically for untreated cases.

Examination of the clinical details in these 5 instances of overdiagnosis will serve to illustrate some of the problems in the clinical diagnosis of thromboembolic phe-

LOCATION OF EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS AT AUTOPSY

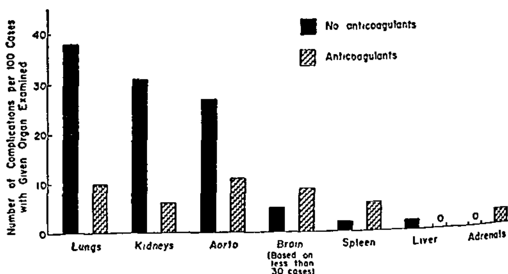


Figure 172. LOCATION OF EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS AT AUTOPSY: Number of extracardiac thromboembolic complications found per hundred cases receiving and not receiving anticoagulants in organs of a given type examined at autopsy.

diac ruptures. A few clinicians[207, 214] have emphasized these risks as deterrents to anticoagulant therapy. Although the degree of risk involved is difficult to evaluate, the importance of the problem warrants a close examination of the autopsy findings. The following sections attempt such an examination and deal, in sequence, with cardiac ruptures, with other intracardiac hemorrhages in rupture cases, with intracardiac hemorrhages in nonrupture cases, with hemorrhages outside the heart, with the completeness of clinical diagnosis of hemorrhage, and with the role of hemorrhages and cardiac ruptures in the death of the patient

Cardiac Ruptures

As has often been demonstrated, cardiac ruptures occur not infrequently in the absence of anticoagulant therapy. In the present series, cardiac ruptures found at autopsy, including incomplete and septal ruptures, numbered 4 among the 48 cases that had received no anticoagulants and 8 among the 41 cases that had received anticoagulants. Details by subclasses are given in Table 166 and case by case in Appendix F, Table 91, case numbers 6, 18, 22, 24, 25, 29, 40, 49, 61, 62, 74, and 84 The meaning of this difference by treatment groups is difficult to *interpret* It cannot be shown to be statistically significant as defined in Appendix C, but this fact is not very meaningful for small samples since very large differences are required for such series before statistical *significance* can be demonstrated

Explanation of the meaning of these differences is further complicated by the fact that anticoagulants reduce the total number of nonrupture *deaths* but not the number of rupture deaths with the result that the number and types of cases coming to autopsy are affected. *Even if* no difference associated with therapy occurs in the case of ruptures, this change in the total number of deaths will increase the proportion of autopsy cases showing rupture in the treated group. By experimentation with the following hypothetical example, the reader can readily demonstrate to himself that this is the case.

Example: Let it be assumed arbitrarily (1) that two groups of 1000 patients each with myocardial infarction have been followed, (2) that one group had received anticoagulants while the other had not, (3) that 3 per cent of the patients in each group died of cardiac rupture, (4) that 10 per cent in each group died of miscellaneous causes, (5) that the only difference was that 12 per [illegible]

cases dying *from each cause* were examined at autopsy. By simple arithmetic one then arrives, on the basis of these assumptions, at the conclusion that 12 per cent of the control group autopsy sample showed rupture as contrasted with 18 per cent of the treated autopsy sample. This contrast has occurred in spite of the fact that in this example *no* difference was postulated in the original incidence of rupture. The arithmetic details are as follows:

	Number of deaths	
	Control group (1000 cases)	Treated group (1000 cases)
Cardiac rupture (3%)	30	30
Miscellaneous causes (10%).	100	100
Thromboembolic complications (12% and 4% respectively)	120	40
Total deaths	250	170
Total autopsies (50% of deaths)	125	85
Total cases with rupture at autopsy.	15	15
Percentage of autopsied cases with rupture	12%	18%

Mainland[119] has discussed at some length the risk of fallacious conclusions from autopsy data and has published illustrations of analogous situations.

In view of this problem, evaluation of rupture deaths in [illegible]

When the misses and the overdiagnoses are balanced one against the other (see again Table 163), the net error in clinical diagnosis (omitting diagnoses which could neither be confirmed nor disproved) for cases not receiving anticoagulants became −50, or more than one miss per case, and for cases receiving anticoagulants, −13, or about 1 miss to each 3 cases examined. Altogether, 5 times as many thromboembolic complications actually had occurred in autopsy cases not receiving anticoagulants as were reported clinically, whereas only twice as many actually had occurred in autopsy cases that had received anticoagulants as were diagnosed clinically. If this difference was characteristic also of cases not dying or not examined at autopsy, the understatement in the clinical findings reported in Chapter VIII is greater in the control than in the treated group. *Since, in spite of the greater degree of understatement for the control group, markedly higher thromboembolic complication rates were observed for the control group, there seems to be little grounds for doubting the effectiveness of anticoagulants as a preventative of thromboembolic phenomena.*

This marked difference in the degree of understatement for the two groups naturally raises the suspicion that perhaps the treated group was observed clinically with greater care than the control group, or that the control group was examined at autopsy more carefully than the treated group. The second of these possibilities was refuted (page 393). The first interpretation also need not be postulated as a general pattern. Consideration of the details suggests that probably all of the following three factors contributed to the observed result: (1) Since single infarctions in the lungs and kidneys are very difficult to distinguish clinically from multiple infarctions of these organs, the fact that such multiple incidents occurred more frequently without anticoagulants than with them would lead also to an increase in the extent of understatement of complications with untreated cases. (2) Since it is practically impossible to diagnose thrombi of the aorta clinically unless the artery is completely occluded, the greater frequency of such thrombi in the absence of anticoagulants would tend to increase the number of misses of such thrombi in untreated cases. (3) Since anticoagulants may increase the likelihood of gross bleeding in the presence of lung or renal infarctions, more frequent clinical recognition of such infarctions might be expected in treated cases. (4) The more frequent urine tests done to detect microscopic hematuria in patients receiving anticoagulants would result incidentally in revealing clinically a higher proportion of existing renal infarctions in such cases than in those not receiving anticoagulants. In addition to being plausible, these interpretations are consistent with the fact that (excluding the legs) the ratio of misses in untreated to misses in treated autopsy cases was highest for the kidneys, next highest for the lungs, and third highest for the aorta (see Appendix F, Table 89). The difference in the degree of understatement in the two treatment groups need not, therefore, lead one to postulate any general difference in diagnostic watchfulness for the two groups. Though a difference of this type is also possible, it has not been evident in other autopsy comparisons with clinical findings. Moreover, even if it did occur, it is obvious that the favorable results for thromboembolic complications associated with anticoagulant therapy were sufficiently marked to be apparent in spite of this greater degree of underreporting for untreated cases.

RUPTURES AND HEMORRHAGES FOUND AT AUTOPSY[a]

The reverse side of the balance sheet for anticoagulant therapy is exhibited by the autopsy findings for hemorrhages and car-

[a] These and other selected findings based on the autopsy analysis were first presented orally by Dr. I. S. Wright at the April, 1953 meeting of the American College of Physicians in Atlantic City.

pears insignificant. Pending further studies, therefore, judgment as to an association between cardiac rupture and anticoagulant therapy must be suspended.

Ruptures in the group receiving no anticoagulants were predominantly ruptures of the septum while those in the group receiving anticoagulants were primarily ruptures of the myocardium of the left ventricle. Three of the myocardial ruptures were complete ruptures in the case of those receiving anticoagulants while the only myocardial rupture among those who had received no anticoagulants was incomplete. In addition, of those who had received anticoagulants and died of rupture, all died in the first or second week of their illness—6 of the 8 within the first week, whereas all those who received *no* anticoagulants and died of rupture died *after* the end of the second week. While all these counts are individually very small and subject to a wide margin of chance fluctuation, the combination of events does suggest one or more of the following: (1) some facilitation of early rupture by anticoagulant therapy, (2) some difference in the typical mechanisms by which it occurs, or (3) confusion by reason of atypical findings for untreated cases.

Examination of other identifiable characteristics of rupture cases yielded various observations of interest. *Counts by sex were consistent with the previously observed greater incidence of rupture in women.*[167, 167] While only 29 per cent of the cases examined at autopsy were women, 7 of the 12 ruptures occurred in women. A further check of the cases suggested a possible explanation for this sex difference in ruptures. Of the 12 rupture cases, facts as to previous hypertension were available for 10, and of these 10, *all but one* (a control case with a septal rupture) *had a history of hypertension*. Since women with myocardial infarction apparently have a history of hypertension much more frequently than men (see Chapter IV), the important factor in the high incidence of rupture in women may not be the sex factor as such but rather, previous hypertension. In view of the very small sample, this observation must, of course, be considered suggestive only. Since the records do not give evidence of any consistent increase in blood pressure immediately preceding the rupture, the relationship appears to operate indirectly through the cumulative effect of prolonged hypertension on the heart walls. Other investigators, such as Howell and Turnbull,[44] have stressed the danger of rupture when sustained hypertension is present after the infarction.

Another factor common to the rupture group was a relatively large infarcted area. Except for one septal rupture for which the size of the infarction could not be classified, all the rupture cases were reported with descriptions indicating that they were extensive, or massive, or, at least exceeded 2 cm. in their largest dimension. The causal connection between the size of the necrotic area and the chance of rupture is obvious. *These observations suggest that cases with a history of hypertension and/or a large infarction should be handled with particular care to forestall cardiac rupture.*

An examination of the clinical record for the rupture cases that had received anticoagulants revealed that *the rupture was, in most cases, a very early development, occurring in 6 of the 8 rupture cases before the 4th day of anticoagulant therapy.* In these 6 cases the highest recorded prothrombin reading was 27 seconds (converted) and only two readings even reached the lower margin of the optimal therapeutic range. Although critical readings, such as those for the day of death, were missing in some cases, and were never available for the exact moment of rupture, *there is certainly no evidence that excessive hypoprothrombinemia as usually defined for anticoagulant therapy played any role in* [illegible]

[illegible] bleeding into the in-

of patients receiving or not receiving anticoagulants in the total sample (612 and 419 respectively, including exceptions) is less likely to be misleading than the use of autopsies as a base, but is subject to the difficulty that counts of ruptures in nonautopsy deaths are lacking. If, in order to use this method, one assumes arbitrarily that the proportion of ruptures in cases not examined postmortem is the same within treatment groups as was revealed at autopsy,* the estimated percentage of the total group that received no anticoagulants and died with rupture present becomes 1.9 per cent as compared with 3.0 per cent for those who received anticoagulants. The difference ap-

* This assumption may exaggerate the incidence of rupture because physicians may have worked harder than usual to secure autopsy permission in rupture cases because of their dramatic character

TABLE 166

RUPTURES OF THE HEART FOUND AT AUTOPSY: Number of Autopsies in Which Various Types of Cardiac Rupture Were Found among Cases Receiving and Not Receiving Anticoagulants, by Time of Death

Type of Rupture and Time of Death	Autopsy Cases Not Receiving Anticoagulants (43 Cases)	Autopsy Cases Receiving Anticoagulants (41 Cases)			
		Total	Day of Anticoagulant Therapy on Which Death Occurred		
			2nd Day	3rd Day	After 3rd Day
Cases dying during first week of illness showing:					
Complete rupture	—	2	—	1	1
Incomplete rupture[a]	—	4	2	2	—
Rupture of septum	—	—	—	—	—
Total ruptures in cases dying during first week	—	6	2	3	1
Cases dying from the second through the sixth week of illness showing:					
Complete rupture	—	1	—	—	1
Incomplete rupture[a]	1	—	—	—	—
Rupture of septum	3	1[b]	—	—	1
Total ruptures in cases dying second through the sixth week	4	2	—	—	2
Total cases with rupture dying within six weeks:					
Complete rupture	—	3	—	1	2
Incomplete rupture[a]	1	4	2	2	—
Rupture of septum	3	1	—	—	1
Total ruptures[c]	4	8	2	3	3

[a] All incomplete ruptures extended into the pericardium

[b] Perforation of the septum may possibly have been congenital in this case.

[c] For full details on individual cases of rupture, see Appendix F Table 91, Case Nos. 6, *18*, *22*, *24*, *25* 29, 40, 49, 61, 62, 74, and 84

rupture deaths by anticoagulant therapy previously mentioned.

Other Intracardiac Hemorrhages in Rupture Cases

The rupture cases previously discussed also showed other types of bleeding closely associated in many cases with the rupture process itself. Typically, the sequence was reconstructed as follows: (1) softening of the necrotic area with or without hemorrhage followed by (2) a rupture under pressure at the site of the infarction, followed by (3) extensive hemopericardium. As would be expected, all cases of myocardial rupture also showed hemopericardium. In addition, one case that had received no anticoagulants developed hemopericardium accompanying a perforation of the interventricular septum (occurring through a fresh myocardial infarction). Thus the total [illegible]

and 7 in cases receiving anticoagulants).

As would be anticipated, the rupture cases, in addition to hemopericardium, showed bleeding at various other intracardiac sites. In some cases this bleeding appeared related to the rupture process while in others the relationship, if present, was not clear from the record. The relationship was most obvious in the case of hemorrhagic original infarctions found at or near the site of the rupture. Of these there were 4 (1 microscopic only) among the 8 rupture cases that had received anticoagulants and 1 among the 4 cases that had not. Among these treated cases was also a case with a massive subepicardial hemorrhage related to the onset of the rupture. In addition, 4 of the 8 rupture cases that had received anticoagulants showed interstitial hemorrhage outside the infarcted area (1 microscopic only), 2 cases showed subepicardial hemorrhage (1 associated with an epicardial hemorrhage), 1 case showed a microscopic epicardial hemorrhage without subepicardial involvement, and 1 case, a subintimal hemorrhage. The relation of these latter hemorrhages to the rupture process was not clear. The 4 rupture cases that had not received anticoagulants included 1 case with a blood-tinged hydropericardium, but no other intracardiac hemorrhages except the one hemorrhagic infarction and 2 hemopericardium cases previously mentioned. This low record for other intracardiac hemorrhage in untreated cases probably is related to the fact that 3 of the 4 ruptures in cases not receiving anticoagulants were septal ruptures.

Since other intracardiac hemorrhages in rupture cases were frequently either the direct antecedent of the rupture process itself or the direct consequence of it (i.e., hemopericardium), the inclusion of these instances of bleeding in other counts of intracardiac hemorrhage would have resulted in some cases in double or triple counting of the same basic episode. This result has been avoided by considering the rupture and nonrupture cases in separate sections.[a] A synthesis on a case count basis is provided in Table 169, Figure 175, and the related textual discussion (pages 433-435).

Intracardiac Hemorrhages in Nonrupture Cases

The findings for specific types of intracardiac hemorrhages in the 44 untreated and 33 treated nonrupture cases examined at autopsy are presented in detail in Table 167 and Figure 174. In general, the major differences possibly associated with anti- [illegible] predominate. [illegible] the autopsy sample

[a] Totals for bleeding in specific areas of the heart that include rupture cases can be computed by adding the counts reported in the above paragraphs to those in Table 167. Before percentages are figured, rupture cases should then also be added to the base counts. Such data would, however, be [illegible]

farcted area as soon as the prothrombin time became moderately prolonged. The opinion of the pathologist on one of these 6 cases, a *patient who died on the second day* of anticoagulant therapy (3rd day after onset), reads, for example, as follows:

> I do not think the extension of the circulation into the wall of the heart was a sudden rupture of the heart, but rather a slow burrowing process with time for hemosiderin to separate out in the older clot formation (probably over a period of a week). Even the oozing into the pericardium must have been prolonged since there is blood pigment there also and some reacting cells. There was possibly a larger gush of blood into the pericardium through the myocardium just before death.

The other two patients with rupture died on the 6th and 10th day of anticoagulants respectively. Both had shown prothrombin times reaching 50 to 59 seconds (converted) and had been treated for excessive hypoprothrombinemia clinically with vitamin K and in one case, with fresh blood. While the exact role of anticoagulants in producing these ruptures cannot be determined, it is certainly advisable to remain alert to the possibility that even mild degrees of hypoprothrombinemia may increase the likelihood of cardiac rupture.

Evaluation of the role of anticoagulants in producing ruptures is further hampered by the low frequency with which ruptures are identified clinically. Only two ruptures, or 17 per cent of the total, were correctly diagnosed clinically in the present series. Both were perforations of the interventricular septum. Rupture was suspected clinically in one other case but was not confirmed at autopsy. Instead, a small pulmonary embolus was found. The cause for sudden death in one other case was given as "unknown—best possibilities myocardial rupture, terminal arrhythmia" but this case was not examined *postmortem*.

In the light, then, of this considerable margin of error in the clinical diagnosis of ruptures, autopsy findings are obviously the only data of value for assessing the frequency of cardiac rupture with antic agulant therapy. Since autopsy data fo treated cases may be expected to reflect reduced number of deaths due to throm boembolism, they are bound also to show greater *proportion* of deaths due to ruptur since anticoagulants cannot prevent rup tures.

This same difficulty unavoidably prevent unequivocal deductions from rupture find ings in other series employing control an treated groups. Previous autopsy series fo myocardial infarction cases not treated wit anticoagulants can, however, be used to tes whether the proportion of ruptures in eac treatment group is similar to previous ex perience without *anticoagulants. If 13 suc* series covering cases not treated with anti coagulants are pooled,[o] the percentage o myocardial infarction *cases examined* a autopsy and found to show rupture becomes 7.6 per cent. This is probably low since in some series rupture of *the* septum was not listed as heart rupture.[p] If, *in* spite of this downward bias, this figure is, nevertheless, assumed to be the true proportion of cardiac ruptures to be expected at autopsy without anticoagulants, the percentage of rupture cases among those not receiving anticoagulants in the present series is not significantly different from this proportion. The chances that a percentage of ruptures as high as that in the group receiving anticoagulants would occur by chance in a sample of 41 cases from such a universe are between 5 and 1 in 100 (i.e., significance, "borderline"). There are, however, other explanations for this difference than anticoagulant therapy, such, for example, as the reduction in non-

[o] The studies pooled were those of *Clagett*, Benge and Hooker[43] who reported on a number of studies from the literature, and the studies of McCain, Kline and Gilson[134] and Zinn and *Cosby*[187]

[p] Gans[71], after a review of the literature, reported that 9 per cent of the cases with acute myocardial infarction developed rupture. This figure is surprisingly close to the figure of 8.3 per cent for untreated cases in the present series.

coagulant therapy appeared in the categories for hemopericardium and for subepicardial, subendocardial and interstitial hemorrhages. As in the case of ruptures, the reduction in deaths resulting from anticoagulant therapy would be expected to increase the proportion of hemorrhagic findings at autopsy for the treated group insofar as these intracardiac hemorrhages increased the risk of dying. (Percentages for incidental hemorrhages would not be expected to be similarly affected.) Since, in addition, the samples are

INTRACARDIAC HEMORRHAGE AT AUTOPSY
in Nonrupture Cases

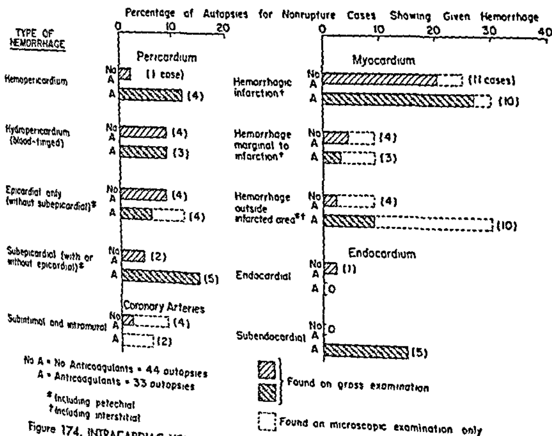


Figure 174. INTRACARDIAC HEMORRHAGE AT AUTOPSY IN NONRUPTURE CASES: Number and percentage of cases found at autopsy to have gross and microscopic intracardiac hemorrhage of various types among cases receiving and not receiving anticoagulants and showing no cardiac rupture at autopsy.

Footnotes for Table 167

[a] One case included in this base count had no microscopic examination of the heart and therefore could not contribute to the totals for microscopic hemorrhages. Percentages may therefore be understated for cases receiving no anticoagulants.

[b] All of these were petechial hem...

[c] One of th...

[d] One case ...

[e] Excludes ... case with subi...

[f] None of t...

...subintimal and intramural hem...

TABLE 167

INTRACARDIAC HEMORRHAGE AT AUTOPSY (NONRUPTURE CASES): Number and Percentage of Autopsy Cases Found to Have Gross or Microscopic Hemorrhages in Various Intracardiac Locations at Autopsy among Cases Receiving and Not Receiving Anticoagulants and Showing No Cardiac Rupture at Autopsy

Location and Type of Hemorrhage	Cases with Intracardiac Hemorrhage											
	Number of Cases						Percentage of Cases					
	Cases Not Receiving Anticoagulants (44 Cases)[a]			Cases Receiving Anticoagulants (33 Cases)			Cases Not Receiving Anticoagulants (44 Cases)[a]			Cases Receiving Anticoagulants (33 Cases)		
	Total	In Gross Report	In Microscopic Report Only	Total	In Gross Report	In Microscopic Report Only	Total	In Gross Report	In Microscopic Report Only	Total	In Gross Report	In Microscopic Report Only
Pericardium:												
Hemopericardium....	1	1	—	4	4	—	2	2	—	12	12	—
Hydropericardium (blood-tinged) .	4	4	—	3	3	—	9	9	—	9	9	—
Epicardial hemorrhage (without subepicardial) . ..	4[b]	4[b]	—	4	2	2	9	9	—	12	6	6
Subepicardial hemorrhage:												
With epicardial.	2[c]	2[c]	—	3	3	—	5	5	—	9	9	—
Without epicardial.	—	—	—	2	2	—	—	—	—	6	6	—
Total with subepicardial hemorrhage	2[c]	2[c]	—	5	5	—	5	5	—	15	15	—
Myocardium:												
Hemorrhagic infarction	11	9	2	10	9	1	25	20	5	30	27	3
Hemorrhage marginal to infarction .	4	2	2	3	1	2	9	5(4 5)	5(4.5)	9	3	6
Hemorrhage outside infarcted area:												
Interstitial .	3[d]	1[d]	2	10	3	7	7	2	5	30	9	21
Petechial .	1[d]	1[d]	—	—	—	—	2	2	—	—	—	—
Type not specified	1	—	1	—	—	—	2	—	2	—	—	—
Total with hemorrhage outside infarcted area (unduplicated)..	4	1	3	10	3	7	9	2	7	30	9	21
Endocardium:												
Endocardial hemorrhage ..	1	1	—	—	—	—	2	2	—	—	—	—
Subendocardial hemorrhage .	—	—	—	5	5	—	—	—	—	15	15	—
Coronary arteries[e]*:*												
Subintimal hemorrhage. . . .	2	—	2	2	—	2	5	—	5	6	—	6
Intramural hemorrhage with arteritis . .	2	1	1	—	—	—	5(4.5)	2(2 3)	2(2.3)	—	—	—
Total with hemorrhage in coronary arteries[f].. ...	4	1	3	2	—	2	9	2	7	6	—	6

footnotes for Table 167 on next page

obliterated by fibrous adhesions intermingled with fresh granular blood *clots*." The epicardium was "mottled by petechial hemorrhages." Unclotted bloody fluid was not found as in the treated cases.

These three treated cases illustrate the development of unrecognized hemopericardium under dicumarol therapy in the absence of excessive prothrombin times. While these deaths cannot be attributed solely to anticoagulants, the cases do illustrate the fact that *with active anticoagulant therapy, hemopericardium is apt to be uncontrolled.*

Similar cases of hemopericardium with tamponade under anticoagulant therapy have also been reported by Nichol,[142] Goldstein and Wolff[75] and Hammarsten.[81] Moreover, the absence of gross hemopericardium in the only untreated case showing evidence of hemopericardium in this series is consistent with the following conclusions of Goldstein and Wolff, arrived at after a review of the literature and autopsy records at Beth Israel Hospital:

> . . . all reported cases of hemopericardium complicating myocardial infarction were due to rupture of the myocardium or of a coronary vessel . . . Although petechiae and injection of the epicardium were not infrequently noted and in 19 cases slightly blood-tinged pericardial fluid was found, *frank gross* hemorrhage into the pericardial cavity *without rupture* was noted only in bishydroxycoumarin-treated patients The conclusion appears warranted that in these cases bishydroxycoumarin was at least partly responsible for the hemopericardium. (Italics not in original)

In view of the occasional occurrence of this serious complication of anticoagulant therapy in myocardial infarction, physicians using anticoagulant therapy should be prepared to recognize hemopericardium by means of physical examination, x-ray and electrocardiogram prior to the death of the patient. According to Goldstein and Wolff, a diagnosis of hemorrhagic pericarditis should be suspected in the presence of (1) a prolonged and persistent or recurrent friction rub, (2) recurrence of cardiac pain, (3) vascular collapse accompanied by distended neck veins and (4) demonstration of pericardial effusion. According to Rose, Ott and Maier,[205] friction rub occurring when prothrombin times are in the therapeutic range may be the first sign of pericardial hemorrhage, while cardiac tamponade "is *evidenced* by a rising venous pressure accompanying an increase in heart size, a small thready pulse, and a narrowed pulse pressure, characteristically with a paradoxical quality to pulse and blood pressures. The heart sounds are not necessarily distant." The authors also state, in addition, that "failure following myocardial infarction is most often predominately left-sided as opposed to the almost exclusively right-sided effects of mechanical obstruction in acute tamponade."

When cardiac tamponade has occurred the patient's chances of survival can be considerably improved by pericardial puncture and drainage. Leedham and Orbison[112] have reported a case of traumatic pericarditis that developed cardiac tamponade without rupture under dicumarol therapy and was successfully treated by pericardial aspiration. Syner[230] has also reported relief of tamponade by pericardial aspiration, while Rose, Ott and Maier[205] have described a case of myocardial infarction treated with anticoagulants in which pericardiotomy was successfully used for the treatment of the same condition. These technics can be life-saving and should be available in an emergency to patients receiving anticoagulant therapy.

Hydropericardium (Blood-Tinged)

No difference associated with anticoagulants was observed in the prevalence of blood-tinged hydropericardium at autopsy (see Figure 174). Three cases receiving and 4 cases not receiving anticoagulants, or 9 per cent of each of the groups examined, showed hydropericardium that was blood-tinged. Since a similar lack of difference in the proportion of autopsy cases showing

small and subject not only to large random sampling errors but also to other unknown selective influences, any conclusions are hazardous. Nevertheless, the data considered as a whole do suggest that anticoagulants played some role in hemorrhages of these four types. Differences in other categories were minor or entirely absent. Details for each type of hemorrhage are presented separately in the paragraphs that follow. To avoid repetition, the foregoing qualifications are not repeated with each separate presentation of data.

Hemopericardium

When rupture cases were excluded, one untreated and 4 treated cases showed hemopericardium, or 2 and 12 per cent respectively of the groups examined at autopsy. Hemopericardium was the immediate cause of death in 2 of the 4 cases with hemopericardium treated with anticoagulants and the contributing cause of death in one treated and one untreated case. Details for the three treated cases dying with hemopericardium as an immediate or contributing cause of death (see Appendix F, Table 91, case numbers 66, 78, and 79) were as follows:

The first case received a total of 1150 mg. of dicumarol between the first and thirteenth day of his illness. His last dose (on the 13th day) was 100 mg. On the 15th day, he complained of moderate substernal pain lasting about 30 minutes (prothrombin time 30 seconds, converted). An extension of the original infarction was diagnosed. That evening the patient became pale, sweated profusely, showed a drop in blood pressure, and gradually went into shock. On the following day he showed an increase in prothrombin time to 43 seconds (converted), for which he was treated with 100 mg. vitamin K intravenously, plus 200 cc. of plasma, procedures which reduced his prothrombin time to 25 seconds (converted). He did not respond otherwise to therapy and died the same day. Clinically he showed no demonstrable hemorrhage except some guaiac positive, coffee-ground vomitus on the day of death. At autopsy he showed hemopericardium (600 cc.) and fibrinous and adhesive pericarditis and a fresh secondary infarction.

The second case in which hemopericardium was an immediate cause of death also showed moderate prothrombin times (none higher than 40 seconds, converted). Progress was uneventful until an extension developed on the 23rd day, after which he declined rapidly, showed a blood pressure 0/0 on two occasions, and was comatose and anuric. At autopsy, a moderate amount of fluid and partly clotted dark blood was found in the pericardial sac, which was bound to the myocardium at the apex by fibrinous adhesions. A hemorrhagic infarction, a massive organizing hemorrhage in an area of aneurysmal dilatation, and scattered focal hemorrhages in the interstitial areas were also found. The pathologist commented as follows:

> The markedly hemorrhagic appearance of the infarct and the hemopericardium seem to have been the result of multiple bleeding points in the necrotic myocardium. Hemorrhage is the usual accompaniment of a recent infarct, but it may very well be that the excessive bleeding was a consequence of the attempt to reduce the coagulability of the blood by dicumarol administration.

The other treated case in which hemopericardium contributed to the patient's death had received 12 days of well-controlled anticoagulant therapy. No excessive prothrombin times were reported. At autopsy a massive infarction and 800–1000 cc. of serohemopericardium were found. It was concluded that:

> the recurrence of pain and increased failure on the day of death were due to cardiac tamponade from the hemopericardium. The latter was no doubt made more serious by reason of dicumarol therapy and might be considered a hemorrhagic complication.

The only untreated case showing hemopericardium presented a somewhat different picture. The pericardial sac was "completely

have been implicated in this subepicardial hemorrhage although it is doubtful that this subepicardial hemorrhage contributed to the patient's death.[*] The consequences of anticoagulant therapy in this case should be judged as due to the errors of poor management.

Hemorrhages in, or Marginal to, the Infarcted Area

The differences associated with anticoagulant therapy with respect to hemorrhages in, or marginal to, the infarction appeared minor after the exclusion of rupture cases, as Figure 174 indicates. Hemorrhagic infarctions or interstitial hemorrhages within the infarcted area were found in 11 cases that had received no anticoagulants (25 per cent of that autopsy group) and in 10 cases that had received anticoagulants (30 per cent of that autopsy group). Hemorrhages marginal to the infarcted area were observed at autopsy in 4 cases receiving no anticoagulants (9 per cent) and in 3 cases receiving anticoagulants (also 9 per cent). No attempt was made to measure the relative amounts of oozing in the necrotic area in the two groups since this type of analysis was not feasible with the records available.

While hemorrhagic infarctions did in some cases lead to cardiac rupture (page 425), only one hemorrhage either in, or marginal to, the infarcted area was considered to have contributed to the death of any nonrupture case in either treatment group (the treated case with hemopericardium reviewed on page 428 [illegible]

w [illegible]

in, or marginal to, the infarction is consistent with the findings of Blumgart and his co-workers[24, 25] who reported no differences in intracardiac hemorrhage in experimental myocardial infarction in dogs.

[*] This subepicardial hemorrhage was not tabulated as contributing to death in Table 170

Hemorrhages in the Myocardium outside the Infarcted Area

Hemorrhages outside the infarcted area showed larger differences associated with anticoagulant therapy than did those inside this area. The difference was primarily in the interstitial category. Ten cases that had received anticoagulants (30 per cent) showed such hemorrhages, all interstitial in type, while only 4 cases that had received no anticoagulants (9 per cent) showed hemorrhages in this category, 3 of which showed interstitial hemorrhages. While the contrast in Figure 174 appears substantial, the samples are small and as a result the difference is only of "borderline" significance statistically. Moreover, most of these hemorrhages were insignificant. Two-thirds were microscopic only. Possibly also a more thorough search in cases that had received anticoagulants may have influenced the results.

With the exception of the case with hemopericardium, a hemorrhagic infarction and interstitial hemorrhage discussed on page 428 (second case), none of the hemorrhages in either group was considered to have contributed to the death of the patient. Thus, while association with anticoagulant therapy is suggested by the data, the consequences of such hemorrhages for the patient were usually minimal.

Endocardial and Subendocardial Hemorrhage

A further difference that appears to be associated with anticoagulant therapy is found in Figure 174 in the bars for subendocardial hemorrhage. Among those receiving anticoagulants, 5, or 15 per cent of that autopsy group, showed some subendocardial hemorrhage on gross examination, while among those not receiving anticoagulants, no subendocardial hemorrhage was found. On the other hand, the group that had received anticoagulants showed no

hydropericardium without blood-tinging was observed (page 447), it would seem reasonable to conclude that the role of anticoagulants in hydropericardium is probably minor or negligible although this condition, whatever the cause, is not itself negligible. Hydropericardium that was blood-tinged was not, however, considered to have contributed to the patient's death in any case.

Epicardial and Subepicardial Hemorrhages

Epicardial and subepicardial hemorrhages present an interesting contrast. While epicardial hemorrhages that did not also involve the subepicardium were about equal for the two treatment groups, subepicardial hemorrhages showed a distinct difference associated with anticoagulant therapy (see Figure 174). Epicardial hemorrhages not involving the subepicardium were found in 4 cases that had received no anticoagulants (9 per cent of the corresponding nonrupture autopsy group) and also in 4 cases that had received anticoagulants (12 per cent). None in the treated group as contrasted with all in the untreated group were petechial hemorrhages.

On the other hand, cases with subepicardial hemorrhages (with and without epicardial involvement) numbered 2 (5 per cent) among those who had received no anticoagulants (one a petechial hemorrhage), as contrasted with 5 cases (15 per cent) among those who had received anticoagulants. All subepicardial hemorrhages were observed on gross examination. The contrast associated with anticoagulant therapy in the case of subepicardial hemorrhage, though not definitive for several reasons, including the small size of the sample, does seem suggestive of some relationship, especially since it is repeated for the subendocardium (see pages 431-432).

No epicardial hemorrhage contributed to the death of the patient in nonrupture cases not receiving anticoagulants, but 2 such cases that had received anticoagulants showed subepicardial hemorrhage that perhaps contributed to the patient's death. A review of these two cases indicates that in one case 6 small areas of subepicardial hemorrhage were found with one area of bloody extravasation (the hemopericardium case discussed on page 428, third case).

The other clinical record reveals an unfortunate series of errors. The case (a private patient) was admitted on an even day and would therefore normally have been a control case in this series. However, anticoagulants were administered out of turn (no reason indicated) in spite of the absence of any thromboembolic complication during the illness or any past history of thromboembolic phenomena and in spite of a prothrombin time of 26 seconds (converted) *prior to* the beginning of anticoagulant therapy. This patient received a total of 800 mg. of dicumarol in three doses (300, 300 and 200 mg. on the first, second and third day of anticoagulants respectively). By the fifth day of dicumarol, the patient's prothrombin time exceeded 100 seconds undilute and reached a maximum of 170 seconds undilute on the 8th day (unconverted times). In spite of these very high times and the development and continuance of hematuria, this patient received no vitamin K or blood to counteract the excessive hypoprothrombinemia. The patient died on the 10th day of dicumarol therapy. At autopsy, "numerous small subepicardial hemorrhages" were found "beneath the epicardium" and (microscopically) "scattered areas of hemorrhage in the loose connective tissue beneath the mucosa of the calyces" and "acute hemorrhagic cystitis." The prolonged prothrombin readings prior to the administration of anticoagulants were explained by the autopsy finding of "cardiac cirrhosis of the liver." Thus, while the original infarction in this case was considered the primary cause of death and there were numerous other contributing conditions, anticoagulant therapy must be presumed to

pendent origin. For similar reasons, the docardium and subendocardium were unted as one layer. Even with these conlidations, the involvement of multiple yers did not always mean that multiple pisodes of bleeding had occurred. For this eason the data must be thought of as a omposite of frequency and magnitude ounts and thus as a rough and approximate out perhaps helpful index of the extent of leeding in cases showing some bleeding. The results for nonrupture cases appear in Table 168.[4] Layers showing only microscopic hemorrhage have been included.

[4] Similar counts for rupture cases were not attempted because the significance of multiple layer involvement in rupture cases is doubtful.

TABLE 168

LAYERS OF THE HEART WITH HEMORRHAGE AT AUTOPSY: Number of Cases Showing Gross or Microscopic Hemorrhage in One, Two, and Three Layers of the Heart at Autopsy among Cases Receiving and Not Receiving Anticoagulants (Excluding Rupture Cases)

Number of Layers of the Heart[a] with Hemorrhage	Number of Cases Examined at Autopsy	
	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants
None	17	6
One	25	18
Two	1	6
Three	1	3
Total cases with any hemorrhage	27[b]	27[c]
Total cases	44	33
Average number of layers showing any hemorrhage (gross or microscopic)	7	1 2

[a] For definition of layers, see pp 432–433.

[b] Of these, 5 cases showed only microscopic hemorrhage

[c] Of these, 7 cases showed only microscopic hemorrhage.

Involvement of multiple layers in hemorrhage was clearly more frequent in the group that had received anticoagulants. Multiple layers were found hemorrhagic in 9 treated nonrupture cases, but in only 2 similar untreated cases. In addition, 17 untreated as compared with only 6 treated cases were completely free of evidence of hemorrhage. The myocardium ranked first as the site of hemorrhage; the pericardium, second; and the endocardium, third. *Cases that had received anticoagulants showed an average of 0.7 layers of the heart with hemorrhagic involvement per nonrupture case examined whereas those who had received anticoagulants averaged 1.2 layers of the heart per case.* This difference is statistically significant and thus is probably not due to chance. However, the proportion in the "no hemorrhage" category in the treated group was probably reduced by the effect of anticoagulants on the number of treated cases dying with thromboembolic complications, as previously explained on page 421.

Cases Showing Any Intracardiac Hemorrhage

Since many cases showed two or more types of intracardiac hemorrhage even when no rupture occurred, a better perspective on intracardiac hemorrhage can be obtained from unduplicated counts of the number of cases showing any type of intracardiac hemorrhage. In such overall counts, the rupture cases can also be included since the the danger of duplicate counting of the same basic process is eliminated (counts refer to cases rather than to hemorrhagic areas). The findings on this basis are reported in Table 169 (based on Appendix F, Table 90) and shown graphically in Figure 175. The contribution of these hemorrhages to the death of the patient is discussed on pages 438–442.

The outstanding features of the findings shown in Figure 175 are: (1) the generally

endocardial hemorrhage, while those receiving no anticoagulants included 1 case with endocardial hemorrhage. While the samples are small and the difference is again only of borderline significance, the data, nevertheless, suggest that anticoagulants may have played some role in subendocardial hemorrhage. This relationship is reminiscent of that observed between epicardial and subepicardial hemorrhage.

While all hemorrhages in this category were observed on gross examination, most of them were of minor importance. The following description is typical: "Immediately beneath the endocardium of the posterior portion of the right atrium are numerous small foci of hemorrhage, none larger than 0.2 cm. in diameter." No such hemorrhage was believed to have contributed to the death of the patient.

Subintimal and Intramural Hemorrhages

Differences in the hemorrhages involving the walls of the coronary arteries were again minimal (see Figure 174). Two cases that had received no anticoagulants and 2 cases that had received anticoagulants showed subintimal hemorrhage. In addition, 2 cases that had received no anticoagulants showed intramural hemorrhage. Thus the proportion of each group showing any hemorrhage in the coronary arteries was 9 per cent for the group receiving no anticoagulants and 6 per cent for the group receiving anticoagulants. No hemorrhage of these types in either group produced further infarctions or contributed in any other way to the death of the patient. (Subintimal hemorrhages that produced the original infarction have been excluded from these counts since such hemorrhages could not have been due to anticoagulant therapy.*) The descriptions of these subintimal hemorrhages in the cases that had received anticoagulants were as follows:

Fresh hemorrhage into thrombus and into subintimal layers.

At one point along area of thrombus there is a dark purple crescent within the wall.

The intima has many slit-like spaces and within the intima is an area of hemorrhage.

Those for cases that had received no anticoagulants were as follows:

A small area of hemorrhage in the subintimal region.

At least one area of hemorrhage within the media (at site of thrombus).

The two intramural hemorrhages found in cases not receiving anticoagulants were described as follows:

There is a small intramural reddish-brown discoloration measuring 0.2 × 0.1 cm. in diameter within the arterial wall at the point of occlusion of the lumen [by thrombus].

Chronic arteritis of circumflex and intramural hemorrhage; [*elsewhere described as*] yellowish-brown discoloration of the wall [*at point*] almost completely occluded).

The evidence in the present series thus does not confirm the fears of some physicians that anticoagulant therapy will increase subintimal hemorrhage within the heart.

Layers of the Heart Affected by Hemorrhage

Since case counts for the number with any particular type of intracardiac hemorrhage fail to reflect adequately the extent of the difference associated with anticoagulant therapy, the data were retabulated according to the number of layers of the heart showing either gross or microscopic hemorrhage. For this immediate tabulation the heart was arbitrarily considered to have only three layers: the myocardium, the pericardium, and the endocardium. The epicardium and subepicardium were included with the pericardium since the multiple hemorrhages within these layers were often not of in-

* For these counts, see Table 156.

involved, conclusive results could hardly have been expected. Even if the difference had been statistically significant by the strict definition adopted, doubt would remain since the findings for the treated group are necessarily exaggerated by the selective influence of anticoagulants on the fatality rate, as was previously explained on page 421). Assessment of the degree of this influence by the same procedures as for ruptures is not justified since the counts include many incidental hemorrhages probably not correlated with the risk of death.*

* Use of the total sample as a base seems incorrect in this case since incidental hemorrhages are obviously not confined to cases dying and no sample is available from which the extent of such hemorrhages in cases not dying can be estimated

Thus, while the data suggest that anticoagulant therapy increased the prevalence of intracardiac hemorrhage, the contribution of other nonrelevant factors to the same result can neither be evaluated nor eliminated.

Hemorrhages outside the Heart

In comparison with hemorrhages in the heart, hemorrhages were very infrequently found in other organs, as Table 169, Appendix F Table 90, and Figure 175 demonstrate. Only 8 cases in each treatment group showed any hemorrhage on gross autopsy examination in any organ outside the heart (see Table 170).

Altogether, 537 organs of cases that had received no anticoagulants were reported examined grossly (counts exclude organs

ORGANS SHOWING GROSS OR MICROSCOPIC HEMORRHAGES AT AUTOPSY

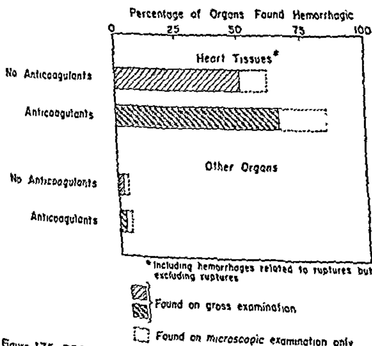


Figure 175. ORGANS SHOWING GROSS OR MICROSCOPIC HEMORRHAGES AT AUTOPSY: Percentage of organs examined both grossly and microscopically at autopsy that were found hemorrhagic on gross examination and percentage found hemorrhagic on microscopic examination only among cases receiving and not receiving anticoagulants.

high prevalence of intracardiac bleeding in fatal myocardial infarction, involving, even in untreated cases, nearly two-thirds (62 per cent)[a] of all cases coming to autopsy when microscopic bleeding is included; (2) the great contrast between the heart and other organs in this respect (62 per cent of the hearts examined but only 4 per cent of other organs in untreated cases showed hemorrhage); (3) the fact that intracardiac bleeding in about 1 in 5 cases bleeding was microscopic, this proportion being slightly higher in treated than in untreated cases; (4) the higher prevalence of intracardiac bleeding among cases that had received anticoagulants than among cases that had not (85 and 62 per cent of these groups respectively).[b]

The first three of these observations reflect the generally high level of intracardiac bleeding in fatal myocardial infarction cases. The subject of the diagnosis and treatment of intracardiac bleeding obviously deserve much greater attention from clinicians than it has received in the past. The fourth observation, that of the contrast associated with anticoagulant therapy, is more difficult to evaluate. Statistical tests indicate that the difference is of borderline significance statistically, but in view of the small samples

[a] One untreated case in which the heart was not examined microscopically was omitted in computing this percentage. Inclusion of this case would have increased this percentage to 63.

[b] If rupture cases are excluded, these percentages become 82 and 61 per cent respectively.

TABLE 169

ORGANS WITH HEMORRHAGE AT AUTOPSY: Percentage of Total Organs in Cases Receiving and Not Receiving Anticoagulants Examined at Autopsy in Which Hemorrhage Was Found on Gross Examination and on Microscopic Examination Only (Cardiac Rupture Cases Included)

Treatment Groups and Organs Examined	Organs Examined Grossly[a]		Organs Examined Both Grossly and Microscopically[c]			
				Percentage in Which Hemorrhage was Found[b]		
	Total Examined Grossly	Percentage in Which Hemorrhage Was Found on Gross Examination[b]	Total Examined Both Grossly and Microscopically	Total	On Gross Examination	On Microscopic Examination Only
Cases receiving no anticoagulants:						
Heart[d]	48	52.1	47	61.7	51.1	10.6
Other organs	537	2.0	450	4.4	2.2	2.2
All organs	585	6.2	497	9.9	6.9	3.0
Cases receiving anticoagulants:						
Heart[d]	41	65.9	41	85.4	65.9	19.5
Other organs	408	2.7[e]	351	5.4[e]	2.6[e]	2.8[e]
All organs	449	8.5	392	13.8	9.2	4.6

[a] Includes organs examined grossly only and organs examined both grossly and microscopically.

[b] For total and specific organs in which hemorrhage was found, see Appendix F Table 90.

[c] Excludes organs examined grossly only.

[d] Excluding cardiac ruptures *per se* but including hemorrhages associated with rupture and other intracardiac hemorrhages in rupture cases.

[e] When percentages were recomputed for the group receiving anticoagulants by a method which gave specific organs the same proportionate weight as in the group not receiving anticoagulants, changes in percentages were minimal (never more than 0.1 percentile points).

ion: 2, lungs (including hemothorax); 2, gastrointestinal tract (diffuse); 1, duodenum; 1, stomach; 1, pancreas; 2, kidneys; and 2, bladder. Corresponding counts for cases that had received anticoagulant therapy were: 1, lungs; 2, large and small bowel; 1, stomach; 3, kidneys; 1, gallbladder; 1, testes; 1, uterus; and 1, ascending aorta (petechial hemorrhage). Many of the hemorrhages in both treatment groups were obviously due to other causes than hypoprothrombinemia induced by anticoagulant therapy. As this listing indicates, counts were also small in all cases and differences for specific organs were neither striking nor significant. Figures for microscopic hemorrhages, which are excluded from the foregoing counts, appear in Appendix F, Table 90.

An examination of hemorrhages found in cases that had received anticoagulants for which no specific etiology was reported and which may thus have been related to anticoagulants revealed that most of these hemorrhages were minor or insignificant. They were variously described as "slight hemorrhagic areas" (testes), "scattered submucosal petechiae" (gallbladder), "several small areas of isolated hemorrhage" (pancreas), "scattered areas of hemorrhage in mucosa" (large and small bowel), "scattered areas of hemorrhage in loose connective tissue beneath mucosa of calyces" (kidneys), etc. One case showed diffuse but microscopic hemorrhages in the lungs, suprarenal and perisuprarenal fat and aortic adventitia (from venules and capillaries). This patient died on the third day of anticoagulants and had received both 150 mg. of dicumarol and 150 mg of heparin on the day prior to death The most severe hemorrhage with no other etiology to explain it was found in a patient with 300 cc. of thick dark red or brown contents in the stomach. Varying amounts of this same material were found throughout the gastrointestinal tract and the mucosa, especially near the pylorus, was hemorrhagic. This patient's prothrombin times had not been excessive.

No extracardiac hemorrhage was considered the immediate or contributing cause of the death of any patient in either treatment group examined at autopsy. In addition, as far as could be determined, extracardiac hemorrhage played no role in the death of any patient not examined at autopsy. *Thus, if this sample is typical, intracardiac hemorrhage and rupture, rather than extracardiac hemorrhage, constitute the major risks of anticoagulants in myocardial infarction.*

Clinical Diagnosis of Hemorrhage

As in the case of thromboembolic complications, the clinical diagnoses of hemorrhage were not closely correlated with the hemorrhagic findings at autopsy (see Figure 176). (See also Appendix F, Table 91 for comparisons case by case.) Failures to diagnose the development of hemorrhage were highest for intracardiac hemorrhage, a very common finding at autopsy. Although 54 cases (excluding rupture cases) showed some degree of intracardiac hemorrhage on either gross or microscopic autopsy examination, none of these hemorrhages was diagnosed clinically. The record was little better for extracardiac hemorrhages. Only 4 of the 42 organs outside the heart reported hemorrhagic on either gross or microscopic autopsy examination had been reported clinically as a source of bleeding, and in one of these the bleeding had been classed as inconsequential by the definition adopted ("occasional red blood cell" per hpf). All of these four correct diagnoses were cases that had received anticoagulants Probably these cases were watched for bleeding more meticulously than untreated cases and the bleeding may also have been more obvious. In other instances, the underlying process had been correctly diagnosed clinically, as for example, an infarction, cystitis, gastritis, congestion, etc., but the presence of bleeding had not been noted clinically. *If this*

infrequently examined). Of these, 11, or only 2.0 per cent, were found to show some *degree of hemorrhage on gross examination.* These hemorrhages were reported associated with such conditions as infarction, congestion, gastritis, cystitis, etc. The prevalence ratio for cases receiving anticoagulant therapy was only slightly above that for untreated cases. Eleven, or 2.7 per cent, of the 408 corresponding organs examined in cases receiving anticoagulants showed some degree of hemorrhage grossly. As in the untreated group, these hemorrhages were commonly associated with infarctions or congestion.

When hemorrhages found only on microscopic examination were included, the counts were approximately doubled. Hemorrhage was found only on microscopic examination in 2.2 per cent of the organs examined in cases receiving no anticoagulants and in 2.8 per cent of the organs examined in cases receiving anticoagulants. When these minute hemorrhages were added in and ratios were based on organs examined both grossly and microscopically, the percentage of organs reported showing any degree of hemorrhage, no matter how minute, became 4.4 for untreated cases and 5.4 for treated cases examined at autopsy. *The risk of extracardiac hemorrhage of the type leaving residual evidence at autopsy seems slight.*[a] *Moreover, in about half the instances in which they occurred, such hemorrhages were so insignificant as to be detected on microscopic examination only.*

These foregoing figures pool the data for the various organs in a single total for each treatment group. This procedure does not appear to have hidden any significant differences for specific organs. Among cases that had received no anticoagulants, the following numbers of cases showed hemorrhage in specified organs on gross examination-

[a] This conclusion seems valid in spite of the selective factors influencing the autopsy sample since the known selective factors were such as to *increase* the treated group percentage of hemorrhage (see p. 421).

TABLE 170

RELATION TO DEATH OF HEMORRHAGE OR RUPTURE FOUND AT AUTOPSY: Number of Cases Receiving and Not Receiving Anticoagulants Showing Hemorrhage or Rupture in the Heart or Hemorrhage outside the Heart on Gross Autopsy Examination, by Relation of Hemorrhage or Rupture to Death

Status of Therapy and Organ Examined	Number of Autopsy Cases Examined Grossly	Number of Cases Showing Hemorrhage or Rupture on Gross Examination		
		Total	Hemorrhage or Rupture an Immediate or Contributing Cause of Death	Hemorrhage an Incidental Finding
Cases not receiving anticoagulants:				
Heart (including both rupture cases and ruptures).	48	26	5	21
Any other organ	48	8	—	8
Total, any organ (unduplicated)	48	30	5	25
Cases receiving anticoagulants				
Heart (including both rupture cases and ruptures)	41	28	11	17
Any other organ	40	8	—	8
Total, any organ (unduplicated)	41*	34	11	23

ity were microscopic or at least not significant to the ultimate outcome for the patient. The really important issue clinically with respect to hemorrhages under anticoagulants, however, is not the risk of minor or microscopic hemorrhages, which may in some cases be numerous without influencing significantly the patient's prospects for survival or satisfactory recovery, but rather the risk of hemorrhage of sufficient severity to be the immediate or contributing cause of death. Because of the importance of this issue, Table 170 has been prepared even though it required decisions as to the role of a given hemorrhage in the death of the patient that were difficult or controversial in a few borderline instances.[7] To facilitate an integrated appraisal, Table 170 reports the total number *of different* autopsy cases in which *any hemorrhage in any part of the body or any rupture in the heart* appeared to have been an immediate or contributing cause of death. Counts include all such hemorrhages found on gross autopsy examination, regardless of etiology, it being too difficult to evaluate accurately in retrospect the role of anticoagulants in producing or aggravating *certain* hemorrhages. On this basis the group of 48 who had received no anticoagulants was found to include 5 cases, and the group of 41 that had received anticoagulants, 11 cases in which hemorrhage or rupture was an immediate or contributing cause of death. Many of the details for these cases have been reported in the various sections relating to specific types of hemorrhage.

The reader will be tempted to convert these counts into percentages and to note that 10 per cent of those autopsy cases that had received no anticoagulants showed at autopsy a hemorrhage that was the immediate or contributing cause of death as contrasted with 27 per cent for those who had received anticoagulants. This is, however, not a satisfactory basis for evaluation since, as previously indicated, the number of cases available for autopsy examination for the treated group undoubtedly was reduced by the prevention of thromboembolic complications by means of anticoagulant therapy, whereas deaths due to hemorrhage could not be expected to undergo any corresponding reduction.*

To secure a base for these counts that would not be affected by the reduction, resulting from anticoagulant therapy, in deaths due to thromboembolic complications, the same technic of appraisal was used as for ruptures (page 422). It was assumed that cases dying but not examined at autopsy were characterized, within treatment groups, by the same proportion of cases with hemorrhage or rupture contributing to death as prevailed among those of the same treatment group actually examined at autopsy.** When estimated on this basis, the proportion of the 419 cases in the total series who received no anticoagulants at any time and

[7] When hemorrhage was a minor incidental factor (as for example, blood-tinged hydropericardium) it was not considered to be a hemorrhage contributing to death in these counts.

* The same type of [illegible] general results of therapy than in the present instance. While this supposition must remain a speculation, no comparable examination of nonfatal cases being possible, the similarity of the treated and untreated groups in many *categories* characterized by relatively minor bleeding (see Table 167 and Figure 174) lends confidence to this inference. In the case of extracardiac *thromboembolic* complications at autopsy, on the other hand, deductions could be more definitive *since* the influence of therapy on the findings on this subject was *in* the main in the opposite direction and was sufficiently strong to be of borderline statistical significance in spite of the counterbalancing effect of anticoagulants on the base count.

** This assumption may lead to overstatement of hemorrhages and ruptures [illegible] since these c[illegible] and would [illegible] normally fo[illegible] permission for autopsy.

sample is typical, clinical reports of the frequency of hemorrhage in myocardial infarction, whether or not anticoagulants are given, clearly understate its true incidence. It is particularly important that physicians using anticoagulants keep strict control of prothrombin levels at all times and stay constantly alert for direct or indirect evidence of bleeding.

A reverse type of comparison of clinical and autopsy findings yields the additional observation that bleeding can be so transient as not to be apparent at autopsy. A review of the clinical records for the cases examined at autopsy revealed that 12 cases showed bleeding clinically (excluding inconsequential bleeding) but were not reported to show hemorrhage in a corresponding organ at autopsy. These included 3 cases with hematuria clinically, 3 cases with hematemesis, and 6 cases with hemoptysis. However, in most instances, underlying pathology that would explain the bleeding was found, for example, bronchopneumonia, renal d ease or infarction, pulmonary congesti etc. Since there can be little doubt th bleeding seen clinically actually occurr it must be assumed that the bleeding w transient and left no evidence. Many cli ically observed hemorrhages occurring und anticoagulant therapy are doubtless of th temporary character. *Thus neither the cli ical nor the autopsy records afford a ful satisfactory basis for the appraisal of the ext of bleeding under anticoagulant therapy— for that matter, in patients who are not und anticoagulant therapy.*

Contribution of Hemorrhages and Ru tures to Death

Most of the data presented thus far ha related to total hemorrhages, irrespective their importance. Of these, the great majo

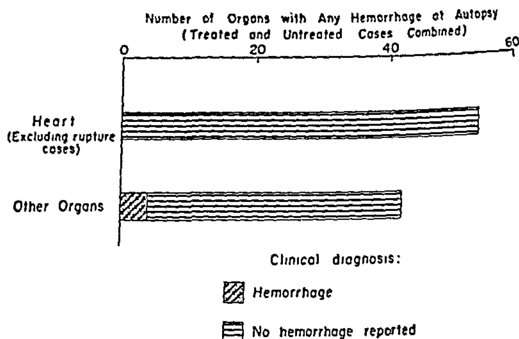


Figure 176. CLINICAL DIAGNOSIS OF HEMORRHAGES FOUND AT AUTOPSY: *Number of total organs examined which were found hemorrhagic at autopsy on gross or microscopic examination, by relation of autopsy finding to clinical diagnosis (excluding cardiac rupture cases).*

this *net* saving there must obviously have been additional savings of 1.7 per hundred cases to counterbalance the losses of 1.7 cases associated with anticoagulant therapy (page 440). The *gross* savings, presumably due to the prevention of thromboembolic complications, can thus be estimated as 9.2 lives per hundred cases (since 7.5 + 1.7 = 9.2)—more than five times the losses to which anticoagulants contributed.

While some[209, 214] contend that this degree of risk is unjustified for patients only mildly ill (good risk cases) whose total death rate may not exceed 2 per cent, this argument fails to take into account the probability that the risk of death from rupture or hemopericardium is undoubtedly also directly correlated with the severity of the case and the general risk of death; for the size of the original infarction, the presence of hypertension and pericarditis, and the general condition of the heart all clearly increase the risk of both rupture and hemopericardium, the two major risks involved. If this is true, the risk that hemorrhage or rupture would contribute to the death of a *good risk* case would thus be considerably below this general 1.7 per cent level. Both the clinical and the autopsy evidence from the present series support this position. That clinically observed hemorrhages were higher among poor than good risk cases was demonstrated in Chapter IX. *Similarly, among all the 16 cases examined at autopsy*

Table 124) One cannot assume, however, that the *total* net savings were *due to* anticoagulants, since chance and other influences may either increase or decrease a difference. Therefore, the words "associated with" have been used above

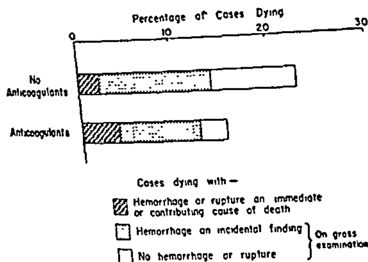


Figure 177. TOTAL DEATHS, BY RELATION OF HEMORRHAGE OR RUPTURE TO DEATH. Percentage of cases dying among cases in the total sample receiving no anticoagulants (419 cases) and cases receiving anticoagulants (612 cases) and estimated proportion of total deaths in which hemorrhage or cardiac rupture was an immediate or contributing cause of death, an incidental finding, or not reported on gross examination. (Proportions were estimated by applying findings at autopsy to total cases dying in each treatment group. For explanation of base counts used, see p. 439.)

who showed hemorrhage or rupture contributing to death became 2.4 per cent, while the corresponding percentage for the 612 cases who had received some anticoagulant therapy became 4.1 per cent. The difference, when evaluated on this basis, is much reduced. If these proportions had, in fact, actually prevailed, they would not have been statistically significant by the definitions adopted for this study (see Appendix C). The deduction that there is no difference associated with anticoagulant therapy is, nevertheless, not warranted, since, with a larger sample, it might well be possible to demonstrate that the true difference between the treatment groups, while small, is nevertheless probably not zero. Caution is particularly indicated in this instance since the observed relationship was in the direction to be expected from the physiological action of anticoagulants and since certain types of less serious bleeding were found higher among treated cases to a statistically significant degree both clinically and at autopsy. *Under the circumstances it is probably safest to conclude that the difference in deaths with bleeding or rupture as a major or contributing factor is probably real, even though small under good management.*

One can carry the process of estimation a step further and use the data from the present series to estimate the difference associated with anticoagulant therapy in the expectancy of death with hemorrhage or rupture as an immediate or contributing cause in myocardial infarction cases of the type studied. On the basis of the estimates previously described, the most probable true difference between such treatment groups as can be randomly represented by this experience can thus be estimated as 1 7 per cent.[bb] *In other words, slightly less than two more deaths with hemorrhage or rupture as a major or contributing cause per hundred cases can probably be expected with anticoagulant therapy than without it. This regrettable loss fortunately is counterbalanced by a substantially lower expectation of death due to thromboembolism with than without anticoagulant protection.* As a result, the net saving in lives associated with anticoagulant therapy reported in Chapter XI was about 7 per hundred hospitalized cases of myocardial infarction.

Figure 177 presents these losses pictorially in their correct setting of *net* gain. The components of the bars consist of three types of cases: (1) cases in which hemorrhage or rupture was the immediate or contributing cause of death, (2) cases in which hemorrhage was found on gross examination but was an incidental finding, and (3) cases with no hemorrhage on gross examination. The components of the bars were estimated, as previously, by assuming that the autopsy findings were typical of all deaths. While hemorrhages and ruptures contributing to death showed a slight increase and incidental hemorrhages were smaller among treated cases only because there were fewer total deaths, *the group dying and showing no hemorrhage* among cases not receiving anticoagulants became, among cases treated with anticoagulants, a group *not dying*.[cc] Since the difference in death rates between the treated and untreated groups is 7.5,[dd] the *net* savings associated with anticoagulants in the present series can be said *to be* 7.5 lives per hundred cases.[ee] To achieve

[bb] Since it is impossible to ascertain whether these autopsied cases actually were similar to nonautopsied cases dying, the accuracy of this estimate cannot be evaluated

[cc] The estimates of the percentage dying with no hemorrhage or rupture were 2 7 for treated cases and 8 6 for untreated cases; those for death with hemorrhage as an incidental finding, 8 6 and 11.9 per cent respectively.

[dd] Percentages used in computing this difference were based on actual deaths among the 419 untreated and 612 treated cases (for reasons explained on pp 392–393) They differ very slightly from the rates quoted in Chapter XI which utilized different bases and procedures.

[ee] The difference between deaths in control and treated groups in 20 other series pooled was substantially greater—14.3 lives per 100 cases (see

matic heart disease with mitral stenosis and insufficiency. The remaining 10 cases (11 per cent) showed mild or moderate sclerotic changes. Thus a total of 99 per cent showed some sclerosis of the coronary arteries. This proportion greatly exceeds those characterizing other arteries in these same patients

Arteriosclerosis was the most common pathological finding reported for the heart valves, involving the aortic valve in 16 of 89 instances and the mitral valve, in 11 instances It is interesting that arteriosclerosis was not noted in any instance in a valve on the right side of the heart, an observation that is consistent with the relatively low findings for arteriosclerosis of the pulmonary arteries.

Aorta

The aorta ranked a close second to the coronary arteries as the site of severe arteriosclerotic changes. Of the 79 cases in which the degree of such changes in the aorta was reported, 96 per cent showed some degree of arteriosclerosis. Severe arteriosclerosis was noted in 43 aortas, or 54 per cent of the total examined. Only 3 (4 per cent) showed no arteriosclerotic changes.

Cerebral Arteries

In contrast to the heart and aorta, mild and moderate rather than severe arteriosclerotic changes were typical of the cerebral arteries, being present in 17, or about half, of the 33 cases thus examined. The other cases were

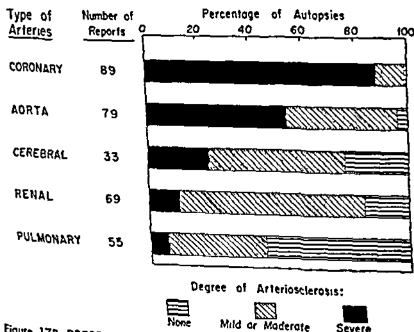


Figure 178. DEGREE OF ARTERIOSCLEROSIS FOUND IN VARIOUS ARTERIES AT AUTOPSY. Percentage of cases found at autopsy to have various degrees of arteriosclerosis in given arteries (cases with no report on arteriosclerosis in given types of arteries excluded).

in the present series in which hemorrhage or cardiac rupture was an immediate or contributing cause of death in either treatment group, all except one were poor risk cases according to Russek's criteria.[209] *With improved procedures for classification, this single case (an 84-year old female with cardiac rupture) would also have been considered a poor risk case since this patient obviously had a large infarction, was hypertensive and was classified as severely ill at onset by the attending physician. The patient did not happen, however, to show any of Russek's signs for discriminating poor risk cases* (page 231).

From the experience in this series appraised both clinically and at autopsy, therefore, it seems highly improbable that the *net* risk of death (i.e., savings balanced against losses) would be increased on the average by the use of anticoagulant therapy in good risk cases *provided* the patients were well screened for contraindications to such therapy and prothrombin times were properly controlled. In view of the protection afforded against disabling and possibly fatal thromboembolic complications, the minimal hemorrhagic risk involved for these patients in anticoagulant therapy seems justified.

DEGREE OF ARTERIOSCLEROSIS FOUND AT AUTOPSY

Because of the great interest in arteri sclerosis and its obvious importance, t autopsy findings in this regard were analyz in some detail. The results are presente organ by organ, in Table 171 and Figu 178. Percentages are based throughout the number of autopsies in which the degr of arteriosclerosis in given organs was r ported. Consequently, since the sampl used necessarily varied from organ to orga comparisons of the findings in one org with those in another are somewhat hazar ous. Where they are attempted, the qual fication "if the sample examined was repr sentative of the total autopsied group must be understood to apply to each suc comparison.

Heart

Severe arteriosclerosis was found most fr quently in the coronary arteries. Seventy eight, or 88 per cent, of the 89 myocardi infarction cases examined at autopsy wer reported to have severely sclerosed coronar arteries. The coronary vessels were free o arteriosclerotic changes in only one instance a case in which there was evidence of rheu

TABLE 171

DEGREE OF ARTERIOSCLEROSIS FOUND AT AUTOPSY · Number and Percentage of Selecte Types of Arteries Examined at Autopsy in Which Mild or Moderate, or Severe Arteriosclerosis Was Found

Type of Arteries	Total Autopsies with Degree of Arteriosclerosis Reported*	Number of Cases				Percentage of Cases			
		Arteriosclerosis Present			Arteriosclerosis Not Present	Arteriosclerosis Present			Arteriosclerosis Not Present
		Total	Mild or Moderate Degree	Severe Degree		Total	Mild or Moderate Degree	Severe Degree	
Coronary	89	88	10	78	1	99	11	88	1
Aorta	79	76	33	43	3	96	42	54	4
Cerebral	33	25	17	8	8	76	52	24	24
Renal	69	57	49	8	12	83	71	12	17
Pulmonary	55	25	21	4	30	45	38	7	55

* Excludes both cases in which the autopsy did not mention the degree of arteriosclerosis and cases in which that part of the cardiovascular system was not examined.

autopsy was compared with the standard heart weight for persons of the same sex and body weight according to the standards published by Smith,[220] the heart weight was found to exceed normal in every instance in which the test could be applied (i.e., the 59 cases for whom both heart and body weight were reported). In 6 instances the excess was less than 75 gm.; in 16, from 75 to 149 gm.; in 19, from 150 to 224 gm.; in 10, from 225 to 299 gm.; and in 8, 300 gm. or more. In an additional group of 27 cases for whom body weight was not reported, the heart weight in all but 3 exceeded normal by Smith's standards for persons weighing 200 pounds.[11] Twelve of these cases of unknown body weight exceeded the norm for 200 pounds by more than 74 gm.

[11] For women the average for 195 pounds (351 cm.) was used since no average for 200 pounds was available.

Previous Myocardial Infarctions

Thirty-two, or slightly more than a third, of the autopsied cases with a recent myocardial infarction showed residual evidence of one or more previous infarctions (see Figure 179). These were evenly divided between the groups receiving and not receiving anticoagulants. This proportion is by no means unusually high. In fact, the proportion with residual evidence of a previous infarction in the present series (36 per cent) is somewhat lower than has been reported in other series. Edmondson and Hoxie[14] found at autopsy that 56 per cent of 865 patients with unhealed infarctions exhibited scars of old infarctions. Lisa and Ring[121] reported that 72 per cent of 32 cases of recent infarctions had evidence of an old infarction, while French and Dock[67] reported that 59 per cent of 80 cases under 40 years of age had suffered a previous infarction

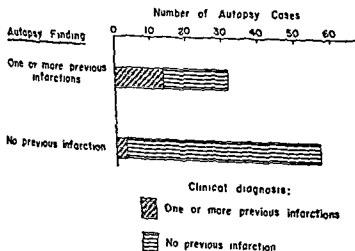


Figure 179. CORRECTNESS OF CLINICAL DIAGNOSIS OF EXISTENCE OF OLD MYOCARDIAL INFARCTIONS: Number of autopsy cases in which one or more old myocardial infarctions were or were not found at *autopsy*, by relation of autopsy finding to clinical *diagnosis* of one or more or no myocardial infarctions occurring prior to the present illness.

equally divided between the severely sclerosed and those with no sclerosis of the cerebral arteries. The low proportion of cases in which the brain was examined is unfortunate.

Renal Arteries

Findings for the renal arteries showed a general similarity to those for the brain. Fifty-seven, or more than 8 in 10, of the 69 cases in which the kidneys were examined, showed some degree of nephrosclerosis at autopsy. Seven-tenths of the cases showed only mild or moderate nephrosclerosis and slightly more than one-tenth, severe nephrosclerosis. Only 17 per cent showed no such changes.

Pulmonary Arteries

The least sclerosis was found in the pulmonary arteries. More than half of the 55 cases in which the lungs were examined showed no hardening of the pulmonary arteries and only 4 (7 per cent) showed severe changes. *The contrast with the severe degree of arteriosclerosis typical of the coronary arteries is striking.* It may well be explained on the basis of the difference in the pressures and hence the work load carried by the lesser circulation.

General Systemic Arteries

In addition to the study of specific organs, an attempt was made to characterize the approximate general level of arteriosclerosis throughout the body, exclusive of the coronary arteries and aorta. In this characterization, consideration was given to the condition of the arteries already mentioned, to the extremities, and to other incidental and generalized references to the subject on the protocol. (Reference to the degree of arteriosclerosis in organs other than those specifically mentioned in the foregoing paragraphs was uncommon. The vessels of only 1 of the livers examined and of none of the spleens or adrenal glands were reported sclerotic.) This generalized approach showed 53, or about three-quarters, of the cases for whom such a characterization could be made to be arteriosclerotic to a mild or moderate degree. Only 12 per cent showed severe generalized arteriosclerosis. This relatively low percentage is in marked contrast to the 88 per cent who showed severe sclerotic changes of the coronary arteries. *The degree of hardening in the coronary vessels is thus distinctly in excess of that in the general systemic arteries. If these cases are typical of the illness, one may conclude that in most cases a selective hardening of the coronary arteries is typical of myocardial infarction cases.*

MISCELLANEOUS FINDINGS WITHIN THE HEART

In addition to the findings relative to the original infarction, the thromboembolic and hemorrhagic complications, the ruptures, and the degree of arteriosclerosis already discussed, various miscellaneous findings within the heart were reported in the protocols. A fairly inclusive listing of these findings is presented in the following paragraphs for any general significance they may have for myocardial infarction. Since they relate exclusively to fatal cases, they probably overstate the pathological characteristics of myocardial infarction as a whole. Insofar as could be ascertained, none of the findings included in this miscellaneous list was the result of either anticoagulant therapy or the lack of such therapy. Consequently, details by treatment received are given only occasionally when they appear helpful as a description of the two samples.

Cardiac Hypertrophy

Cardiac hypertrophy was the rule among those cases in this series that came to autopsy. When the weight of the heart reported at

Hydropericardium

The hemopericardium and rupture findings have been previously discussed and are not repeated here. There remain 29 instances in which some measure of hydropericardium was present. In 8 of these, the fluid in the pericardium was tinged with blood. *The frequency with which fluid was found in the pericardium showed no clear relation to anticoagulant therapy since 13 of the 29 cases had received anticoagulants and 16 had not* (32 and 33 per cent of the respective groups examined at autopsy). The fluid was blood-tinged in 3 cases receiving anticoagulants and in 5 cases not receiving anticoagulants.

Miscellaneous Findings in the Endocardium

A patent foramen ovale was reported in 4 autopsied hearts Some degree of endocarditis was also described in 8 instances, 7 of these being cases that did not receive anticoagulants. A single case in the same category exhibited an old mural thrombus described as antedating the present illness.

Miscellaneous Findings in the Valves

A large variety of valvular deformities and defects were described at autopsy. *Forty-one, or almost half, of the cases examined showed some valvular disease or deformity.* The majority of these conditions were degenerative in character or else the end-results of old, healed inflammatory processes. In most instances these changes were isolated and of no great apparent significance. Healed nondeforming endocarditis was found on all valves in the heart, but was most frequently found in the aortic and mitral valves.

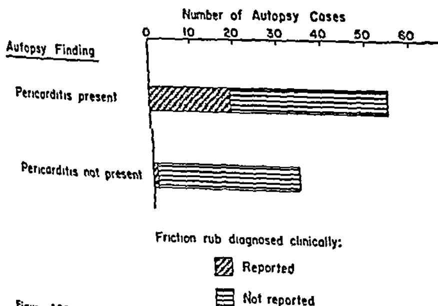


Figure 180. PERICARDITIS AT AUTOPSY IN RELATION TO CLINICAL RECOGNITION OF FRICTION RUB: Number of autopsy cases in which pericarditis was and was not found, by relation of autopsy finding to clinical diagnosis of friction rub.

More surprising, perhaps, is the evidence of underdiagnosis of such infarctions clinically. In only 14, or less than half, of those examined at autopsy in the present series was there any evidence indicating that any previous infarction had been recognized prior to death either in the history or by EKG. This failure to diagnose previous infarctions that had actually occurred was equally frequent among those receiving and not receiving anticoagulants, occurring in both groups in 56 per cent of the autopsied cases with such infarctions at autopsy. Blumgart, Schlesinger and Davis[26] also found that several of their patients believed clinically to have suffered but a single infarction actually had one or more previous infarctions at autopsy.

In this series, the record of diagnosis of previous myocardial infarctions indicated that something over half of such infarctions had never been recognized clinically.

Errors of the opposite type were much less frequent. In only 3 cases among the 57 in the present study for whom no evidence of an infarction prior to the present attack could be found at autopsy, had a diagnosis of such a previous infarction been made prior to death. In even fewer instances (4 cases, or 13 per cent of those with old infarctions) had an old infarction been diagnosed by EKG records during the illness studied. Evidently it is possible for infarctions that are not fatal to heal to the extent that electrocardiographic evidence of their presence is obscured by a subsequent infarction.

Miscellaneous Findings in the Myocardium and Coronary Arteries

Dilatation of the heart, usually of the left ventricle, was noted in 44 reports. Among these fatal cases, differences by treatment received appear unimportant since 19 of these dilatation cases had received anticoagulants and 25 had not. Aneurysm was described in 6 cases receiving anticoagulants and in 9 who had received none. Fibrosis was present in 50 cases, fatty degeneration in 14 cases and atrophy and focal degeneration of the myocardium, in 2 cases each. Reports of findings for old thrombi in the coronary arteries did not correspond with those relative to previous infarctions of the myocardium. As contrasted with 32 cases reported to show old infarctions, references to old thrombi in the coronary arteries believed to antedate the illness were noted in only 16 protocols and other old occlusions, in 6 protocols.

Pericarditis

Pericarditis of some degree was evident at autopsy in 55 instances, or about two-thirds of the cases examined postmortem. Only 19, or 35 per cent of these 55 cases had been reported to show friction rub clinically (see Figure 180). Whether the clinical diagnosis of this condition was actually missed in all these instances, or whether in some cases it was merely unreported, is not known. The reverse type of error, namely, a report of friction rub in a case in which there was no evidence of pericarditis reported at autopsy, occurred in only one instance among the 34 without pericarditis in the present series.

The proportion for the present series (62 per cent) includes all degrees of pericarditis, including mild cases, and is higher than has been reported in several other series. Yater et al.[264] described focal fibrinous pericarditis in 12, and diffuse fibrinous pericarditis in 1, of 84 patients with recent or organizing infarctions examined postmortem, a proportion of acute pericarditis in such cases of 16 per cent. Levine and Brown[113] reported findings of 52 per cent at autopsy, Bean,[11] findings of 28 per cent, and Wolff and White,[247] findings of 48 per cent.

bronchiectasis, in 3 There were also 2 cases of active tuberculosis.

Gastrointestinal Tract

Congestion of the gastrointestinal tract was noted in 19 cases (25 per cent of the 76 cases in which the gastrointestinal tract was examined). The following types of gastrointestinal lesions were observed, each in a single case, among patients treated with anticoagulants: esophageal ulcer, catarrhal colitis, and diverticulosis of the colon. It is of interest that no hemorrhages were found in these patients at these sites in spite of this pathology and the use of anticoagulant therapy. Possible sources of bleeding found in one case each among patients not receiving anticoagulants were: esophagitis, esophageal varices, gastric varices, acute gastric ulcer, polyps of the stomach and colon and carcinoma of the cecum, and 2 cases of diverticulosis of the colon Four cases of active duodenal ulcer were also reported for this group. No hemorrhages were found in these patients at these sites.

Liver, Gallbladder, and Pancreas

Congestion of the liver was noted in 73 instances, or about nine-tenths of the 81 cases in which the liver was examined Other changes were also frequently reported, attesting to the frequency with which hepatic disorders are present in an aging population. These included 21 instances of fatty liver; 7, of cirrhosis; 5, of central necrosis; and 4, of hepatitis. Five instances of hemangioma of the liver were observed, 4 of these of the cavernous type. Cholecystitis was reported in 15 instances and cholelithiasis, in 17 instances, evidence of the frequency of gallbladder disease in the aging population. The pancreas, examined in 79 cases, showed congestion in 6 instances and was the site of fatty infiltration or lipoidosis in 4 cases.

Kidneys, Bladder, and Prostate

Congestion of the kidneys was remarked upon in 45 cases, or in about half of the 80 cases in which the kidneys and bladder were examined. There were 7 old infarctions described and 1 "old embolus." Necrotizing arteriolitis was noted in 1 instance and an unspecified arteritis, in 1 case. Renal disease was also very common. There were 9 instances of pyelonephritis, 2 of pyelitis, 2 of nephrosis, 2 of toxic nephrosis, and 1 of glomerulonephritis. A single case with nephrolithiasis received anticoagulants without bleeding. Cystitis was mentioned in 16 cases and varices of the bladder, in one. Of the 53 prostates examined, 10 were hypertrophied, 11 were hyperplastic, and 5 exhibited prostatitis.

Adrenals and Spleen

The only significant finding in the adrenals was congestion, recorded in 21, or about a fourth of the 77 cases in which the adrenals were examined. The spleen was congested in 61, or three-quarters of the 79 cases in which the spleen was examined. One old embolus and one instance of necrotizing arteriolitis were also mentioned.

Miscellaneous Observations

Subcutaneous edema was noted in 18 cases; ascites, in 7; obesity, in 15; gout, in 2; and staphylococcus septicemia, in one patient

SUMMARY OF AUTOPSY FINDINGS AND CONCLUSIONS

A total of 91 cases from the present series were examined at autopsy (48 per cent of all deaths). The autopsy analysis in the present chapter is based, however, on 89 instead of 91 cases, since in two instances autopsy findings failed to confirm the orig-

MISCELLANEOUS FINDINGS OUTSIDE THE HEART

Aside from arteriosclerosis, discussed separately, a wide variety of pathological conditions outside the heart was also disclosed at postmortem. The majority of those listed appear to have had no particular significance in relation to the patient's final illness and a few were obviously terminal events. There remain a modest number, aside from thromboembolic complications or hemorrhagic phenomena already discussed, which were of undoubted importance in the fatal outcome observed. Those deemed worthy of discussion are listed in the paragraphs which follow, together with a few others of interest because they pertain to the cardiovascular system. No attempt has been made to re-enumerate thromboembolic complications or hemorrhages or to enumerate all miscellaneous complications. With the exception of the hemorrhages previously discussed, none of the miscellaneous conditions, listed or unlisted, appeared to have resulted from toxic effects or organ damage from anticoagulant therapy.

Aorta and Systemic Arteries and Veins

The almost universal occurrence of arteriosclerosis of the aorta in the cases autopsied (in 76 of 79 cases examined postmortem) was accompanied in 31 instances by demonstrable calcification and in 20 instances, by ulceration. The aorta was noted to be dilated in 5 instances—to the point of aneurysm formation in 2 of these 5 cases. There was an unspecified aortitis in 1 instance and syphilitic aortitis in 1 case. No disease was reported in the other systemic arteries other than the arteriosclerosis previously mentioned. Phlebosclerosis was mentioned in 3 protocols. Impairment of the peripheral circulation had produced dry gangrene in one case only.

Brain

There was evidence of chronically impaired cerebral circulation in 8 of the 33 cases in which the brain was examined. This impairment had resulted in cerebral atrophy in 3 instances and in encephalomalacia in 5 instances. One case showed evidence of an old cerebellar infarction and one, a cerebral accident of unspecified type. Cerebral congestion was recorded in 4 instances and cerebral edema, in 5 cases. Of significance in the fatal outcome of the illness studied were the findings of meningitis, of leptomeningitis, and of miliary brain abscesses in one case each. The brain abscesses occurred in a case with staphylococcal septicemia.

Lungs and Pleura

Left heart failure was evident from the lung findings in many cases. There was pulmonary congestion in 73 of the 88 cases in which the lungs were examined, pulmonary edema in 44 cases, and hydrothorax, in 47 cases.[a] Eighteen of these patients developed bronchopneumonia; 10, lobular pneumonia; and one each, hypostatic and lipoid pneumonia. An additional case showed a pulmonary abscess. Whether the latter was the result of pneumonia or pulmonary embolism is not clear. Pulmonary emphysema was recorded in 36 cases; atelectasis, in 21; and fibrosis, in 6. There were 15 cases with fibrinous pleurisy and 2 cases of empyema. Bronchitis was present in 16 cases and

[a] Although the fact that the hydrothorax count exceeds the count for pulmonary edema appears to be a paradox, it is probably due to (1) underreporting of pulmonary edema, (2) full reporting of hydrothorax even in cases where the lungs were not examined, (3) differences in opinion as to what is severe pulmonary congestion and what is pulmonary edema, (4) the fact that hydrothorax can originate from other causes (i.e., pneumonia), and (5) the possibility that pulmonary edema appearing early in the illness and clearing prior to death may have left
cleared at the ti

to miscellaneous or unknown causes. *Only 3.4 per cent of the original infarctions and none of the secondary infarctions or extensions were reported due to subintimal hemorrhage.* Thus, if these fatal cases are typical, the risk that anticoagulant therapy will augment such hemorrhages appears minimal.

Important also in the etiology of myocardial infarction was sclerosis of the coronary arteries. Nine-tenths of the cases examined showed severe sclerosis in these arteries Sclerosis was also nearly universal in the aorta, but was severe in only about half the cases. It was usually considerably less prevalent and also less severe in the general systemic arteries and showed even lower levels in the pulmonary circulation In addition to this handicap of severe coronary sclerosis, slightly more than a third of these fatal cases showed residual evidence of previous infarctions and almost half showed some valvular disease or deformity. Cardiac hypertrophy was universal among all cases in which comparisons with norms was possible. More than half also showed fibrosis of the myocardium and about one half, dilatation of the chambers of the heart.

The consequences of the attack were reflected in pericarditis, evidences of which were found in about two-thirds of these fatal cases, and hydropericardium, found in about one-third. The severely impaired heart action characteristic of fatal cases was reflected also in pulmonary congestion, found in 83 per cent, and in hydrothorax and pulmonary edema, each found in one-half the cases. About a third developed pneumonia, mostly terminally Nine-tenths showed congestion of the liver, one-half, congestion of the kidneys; and one-fourth each, congestion of the gastrointestinal tract and spleen. Other findings, exclusive of hemorrhages, ruptures, and thromboembolic complications, were mostly miscellaneous in character and showed little relation either to myocardial infarction as such or to anticoagulant therapy.

Correctness of Clinical Diagnoses

The autopsy findings were used in the second place to test the correctness of the clinical diagnoses and thus to ascertain the nature and direction of any existing bias in the previously reported clinical findings. The highest record for clinical correctness was achieved in the clinical diagnosis of the original infarctions, 98 per cent of which were confirmed at autopsy. While this high record was facilitated by the omission of doubtful cases from the sample and may exceed the correctness of such diagnoses for nonfatal cases, it does nevertheless give assurance that the group studied probably consisted almost entirely of myocardial infarction cases. Diagnoses of the location of the infarction ranked second in correctness, the location in addition to the presence of the infarction having been correctly diagnosed in 87 per cent of the autopsy cases. Other major diagnoses of interest ranked in descending order of correctness as follows: sixty-three per cent of the extensions and secondary infarctions in the myocardium following the original infarction in the present illness had been diagnosed clinically, but only 44 per cent of the cases with previous infarctions had been so diagnosed. Friction rub had been diagnosed clinically in only 35 per cent of the cases showing pericarditis at autopsy. Only 13 per cent of the extracardiac thromboembolic complications and 10 per cent of extracardiac hemorrhages (including microscopic) had been reported clinically. Finally, none of the mural thrombi, none of the intracardiac hemorrhages, and none of the myocardial ruptures had been diagnosed clinically (all clinically diagnosed ruptures were ruptures of the interventricular septum). Since the cases in the sample were reported by hospitals of outstanding merit and the work was supervised in most instances by expert cardiologists, it is clear that such underdiagnosis reflects primarily the inherent difficulty of recognizing these conditions from evidence

inal diagnosis of myocardial infarction. Of these 89, 41 had received anticoagulants and 48 had not (7 and 11 per cent respectively of the total cases in the two treatment groups clinically). The lower number of treated cases examined at autopsy reflects mainly the difference in deaths associated with treatment, since there was little difference in the proportion of cases dying in the control and treated groups that were examined at autopsy.

Selective Factors Affecting Findings

Consideration of the characteristics of this autopsy sample and the process by which it was selected indicates that selection occurring at the four following stages influenced the findings: (1) general characteristics of the patients and their attacks determined who died and who survived the illness; (2) anticoagulants modified the course of the illness and its outcome only for treated cases and then unequally according to the number of days the patient survived and the details of the therapeutic regimen; (3) a multiplicity of factors determined which patients dying would be examined at autopsy; and (4) the pathologists, subject in many cases to restrictions, selected only certain organs for examination and these they examined with varying degrees of thoroughness.

The need to take into account the effects of these various selective processes on the autopsy findings greatly complicates deductions from autopsy data. *In general in the present study, the first of these types of selection rendered the autopsy sample atypical of myocardial infarction cases as a whole, though possibly representative of severe cases.* The second, by reducing the proportion of treated cases dying from thromboembolic complications and thus the number of such patients examined at autopsy, leads indirectly to an understatement[bb] in autopsy data of the advantages of anticoagulants and an overstatement of its hazards (see page 421). The third type of selection introduced no appreciable bias in the sample that could be tested with available data but may nevertheless have contributed. Whether the fourth type of selection influenced the findings cannot be determined since there is no possible way of knowing what conditions existed in organs not examined. Differences with respect to completeness of examination and fullness of reporting were minor.

General Characteristics of Myocardial Infarction

The autopsy findings were utilized in the main to answer four types of questions, the first of which concerned the general nature of fatal myocardial infarction. Among the salient findings pertinent to this question (excluding those involving thromboembolic complications, ruptures, or hemorrhages) were the following: The left coronary artery was most frequently the site of the occlusion, typically its anterior descending branch. The original infarction in most cases was located in the left ventricle and was more commonly anterior than posterior in location, but frequently involved the septum. *Nearly three-fourths of the original infarctions were due to thrombi, a proportion that also prevailed for extensions and new secondary infarctions.* Thus a maximum of about three-quarters of these infarctions were potentially preventable with anticoagulant therapy, provided the need could have been anticipated and therapy instituted in time. Fifteen per cent of the original infarctions were due to coronary insufficiency rather than to complete occlusion. The remainder (11 per cent) were due

[bb] The presence among treated autopsy cases of somewhat more deaths with cardiac rupture as an immediate or contributing cause of death influenced the findings in the opposite direction (see footnote d, p. 405 and footnote j, p 415). However, this influence is minor in comparison with the combined effect of the factors noted above, as is evident from net savings (p. 440); hence the *net* effect of known influences is clearly in the direction of understatement of benefits.

Findings on Hemorrhagic Complications and Ruptures

The fourth and last major function for which the autopsy findings were used was the re-evaluation with autopsy data of the hemorrhagic and rupture risk associated with anticoagulant therapy. As previously indicated, this is particularly difficult both because of the small samples and because the selection involved in the autopsy sample artificially increased the proportion of cases with fatal hemorrhage (see page 421). Thus, when the data show an increased proportion of hemorrhages in treated cases, it was almost impossible to determine to what extent anticoagulants were directly responsible and to what extent they merely appeared responsible because of their effect of reducing the number of treated group cases dying from thromboembolic phenomena. Bearing in mind this artificial overstatement of hemorrhages in the treated group, the following major findings with respect to ruptures and hemorrhages are itemized:

1. Untreated cases showed 4 cardiac ruptures among 48 cases autopsied. Of these, 3 were ruptures of the interventricular septum. All occurred after the second week of the illness. Treated cases showed 8 ruptures among 41 cases autopsied. Seven of these involved the myocardium. All occurred before the 3rd week

2. To eliminate the influence on these rupture percentages of the reduction in deaths due to thromboembolism, these counts were related to the total number of treated and untreated cases (by assuming that a corresponding proportion of nonautopsy deaths involved rupture). On this basis it was estimated that 1.9 per cent of the untreated cases and 3.0 per cent of the treated cases died with cardiac rupture.

3. In addition to these rupture deaths, 1 untreated and 3 treated cases died with other intracardiac hemorrhage (principally hemopericardium) as an immediate or contributing cause of death When these cases were added to the rupture figures, it was found that a total of 5 autopsy cases that had received no anticoagulants and 11 such cases that had received anticoagulants died with hemorrhage or rupture as an immediate or contributing cause of death. No other deaths in either group could be laid directly or indirectly to hemorrhage or rupture.

4. By a similar application of the findings in item 2 to nonautopsy deaths, it was estimated that 2.4 per cent of all cases that had received no anticoagulants and 4.1 per cent of all cases that had received anticoagulants died with rupture or hemorrhage as an immediate or contributing cause of death. The increase in such deaths was compensated for about five-fold by the reduction of deaths with thromboembolism as an immediate or contributing cause, as the substantially lower total net death rate for treated cases makes evident.

5. Intracardiac hemorrhage, when broadly defined to include minor hemorrhages, was found to be an exceedingly common phenomenon, even in the absence of anticoagulant therapy. Fifty-two per cent of the untreated autopsied cases as compared with 66 per cent of the treated autopsied cases showed some type of intracardiac hemorrhage (other than rupture) on gross examination, and an additional 11 and 20 per cent respectively showed microscopic hemorrhage (Conversion of these and subsequent percentages to total sample percentages, as in items 2 and 4, is inappropriate since the influence of selection through death diminishes with decreasing severity of hemorrhage until, in incidental bleeding, it probably produces no bias.)

6. Untreated nonrupture cases showed an average of 0.7 heart layers and treated cases, 1.2 heart layers involved in gross or microscopic hemorrhage

7. Specific types of intracardiac hemorrhage in nonrupture autopsied cases, when compared in terms of the percentage of autopsy cases with given hemorrhage, showed the following major contrasts:

a. Hemopericardium (2 per cent, untreated, *vs.* 12 per cent, treated).

b. Subepicardial hemorrhage (5 per cent

available prior to death. Nevertheless, it follows inevitably that the clinical findings reported in previous chapters both for thromboembolic complications and for hemorrhages, especially minor ones, greatly understate the incidence of these conditions in fatal cases. It seems reasonable to believe that a similar, though less extreme, downward bias also characterizes the data reported for nonfatal cases. In fact, underdiagnosis of these conditions is probably characteristic of most medical practice.

Underdiagnosis of both extracardiac thromboembolic complications and extracardiac hemorrhages occurred more frequently in cases that had received no anticoagulants than in cases receiving this therapy, a fact that suggests in part that in certain critical respects treated cases were more meticulously observed clinically than untreated cases. Correction for this unequal degree of underreporting would increase the contrasts between untreated and treated cases for thromboembolic phenomena and reduce the contrasts for hemorrhages, thus strengthening the evidence favorable to anticoagulant therapy.

The opposite type of error, namely, the diagnosis of conditions not confirmed at autopsy, was not only very infrequently noted but also so divided between treatment groups that correction for these errors would not alter the conclusions. Moreover, since errors of overdiagnosis were greatly overshadowed by errors of underdiagnosis, there are no grounds for believing that the clinical findings as reported are inflated. The opposite is, in fact, rather clearly the case.

Findings on Thromboembolic Complications

The third function for which the autopsy data were used was the reappraisal on the basis of fuller evidence of the role of anticoagulants in the prevention of thromboembolic complications. The findings for mural thrombi in the heart chambers were particularly striking. *Two-thirds (63 per cent) of the untreated cases but only a third (32 per cent) of the treated cases showed mural thrombi at autopsy. Moreover, 0.8 chambers or appendages showed thrombi in untreated cases as compared with only 0.4 chambers or appendages in treated cases. Both types of differences were statistically significant.* In the absence of anticoagulant therapy, extracardiac thromboembolic complications (emboli and thrombi with and without accompanying infarction) were also exceedingly common. *They averaged 125 per hundred cases examined among cases not receiving anticoagulants but only 45 per hundred among cases receiving anticoagulants.* The organs in which these extracardiac thromboembolic complications were found, listed in descending order of frequency, were: lungs, kidneys, aorta, brain, spleen, liver, and adrenal glands. Thrombi in the veins of the arms and legs and in other veins were also found in a high proportion of the exceedingly few cases thus examined.

Intracardiac extensions and secondary infarctions, on the other hand, showed no difference at autopsy associated with treatment, the percentage with such complications being 27 per hundred cases in both treatment groups regardless of the therapy received. Probably this comparison, like most others involving thromboembolic complications, understates the favorable consequences of anticoagulants. Understatement is, in fact, the inevitable consequence of the following facts: (1) many treated cases in the autopsy sample had received relatively little and often inadequate anticoagulant therapy, (2) cases saved from thromboembolic complications by anticoagulant therapy often did not die and therefore did not appear in the autopsy sample and (3) underdiagnosis of thromboembolic complications was more prevalent in untreated than in treated cases.

When considered as a whole, therefore, the foregoing evidence clearly supports the conclusion that anticoagulants substantially reduce the incidence of thromboembolic phenomena in myocardial infarction.

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2. To eliminate the influence on these rupture percentages of the reduction in deaths due to thromboembolism, these counts were related to the total number of treated and untreated cases (by assuming that a corresponding proportion of nonautopsy deaths involved rupture). On this basis it was estimated that 1.9 per cent of the untreated cases and 3.0 per cent of the treated cases died with cardiac rupture.

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b. Subepicardial hemorrhage (5 per cent, untreated, *vs.* 15 per cent

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The opposite type of error, namely, the diagnosis *of conditions not confirmed at* autopsy, was not only very infrequently noted but also so divided between treatment groups that correction for these errors would not alter the conclusions. Moreover, since errors of overdiagnosis were greatly overshadowed by errors of underdiagnosis, there are no grounds for believing that the clinical findings as reported are inflated. The opposite is, *in fact,* rather clearly the case.

Findings on Thromboembolic Complications

The third function for which the autopsy data were used was the reappraisal on the basis of fuller evidence of the role of anticoagulants in the prevention of thromboembolic complications. The findings for mural thrombi in the heart chambers were particularly striking. *Two-thirds (63 per cent) of the untreated cases but only a third (32 per cent) of the treated cases showed mural thrombi at autopsy. Moreover, 0.8 chambers or appendages showed thrombi in untreated cases as compared with only 0.4 chambers or appendages in treated cases. Both types of differences were statistically significant.* In the absence of anticoagulant therapy, extracardiac thromboembolic complications (emboli and thrombi with and without accompanying infarction) were also exceedingly common. *They averaged 125 per hundred cases examined among cases not receiving anticoagulants but only 45 per hundred among cases receiving anticoagulants.* The organs in which these extracardiac thromboembolic complications were found, listed in descending order of frequency, were: lungs, kidneys, aorta, brain, spleen, liver, and adrenal glands. Thrombi in the veins of the arms and legs and in other veins were also found in a high proportion of the exceedingly few cases thus examined.

Intracardiac extensions and secondary infarctions, on the other hand, showed no difference at autopsy associated with treatment, the percentage with such complications being 27 per hundred cases in both treatment groups regardless of the therapy received. Probably this comparison, like most others involving thromboembolic complications, understates the favorable consequences of anticoagulants. Understatement is, in fact, the inevitable consequence of the following facts: (1) many treated cases in the autopsy sample had received relatively little and often inadequate anticoagulant therapy, (2) cases saved from thromboembolic complications by anticoagulant therapy often did not die and therefore did not appear in the autopsy sample and (3) underdiagnosis of thromboembolic complications was more prevalent in untreated than in treated cases.

When considered as a whole, therefore, the foregoing evidence clearly supports the conclusion that anticoagulants substantially reduce the incidence of thromboembolic phenomena in myocardial infarction.

risk of hemorrhage and cardiac rupture. Fortunately, the resulting dilemma can be resolved by consideration of the following conclusions based on the data which have been analyzed in this study:

1. Fatal hemorrhages and cardiac ruptures are infrequent under well-administered therapy and such losses are compensated for by a savings in lives through the prevention of thromboembolic complications of about five times the losses incurred.

2 The incidence of both major and minor hemorrhages can be minimized by good management of anticoagulant therapy.

3. The consequences of nonfatal hemorrhages associated with anticoagulants are mostly minor, transient, and easily controlled, and usually leave no permanent sequelae.

4. Thromboembolic complications following myocardial infarction constitute a frequent and serious threat and, even when not fatal in their consequences, may produce serious and permanent damage.

5. The likelihood of thromboembolic complications is not individually predictable.

6. Adequate anticoagulant therapy can reduce the incidence of thromboembolic complications to about a third of that prevailing in untreated cases.

7. Though variations in the amount of the reduction occur, these reductions in proportion to untreated levels are approximately similar in all types of cases.

It is therefore recommended that, in order to provide the maximum protection, a substantial period of three to four weeks of anticoagulant therapy be given to patients with myocardial infarction, provided that no significant contraindications are present and that facilities are available for meticulous supervision of its administration.

c. Interstitial hemorrhage outside the infarcted area (7 per cent, untreated, *vs.* 30 per cent, treated). In each group about two-thirds of these were microscopic only.

d. Subendocardial hemorrhage (0 per cent, untreated, *vs.* 15 per cent, treated).

8. Hemorrhages in, or marginal to, the infarcted area of the myocardium and other miscellaneous types of intracardiac hemorrhage showed only minimal increases, no difference, or minor reversals in nonrupture cases.

9. Rupture cases, on the other hand, often showed hemorrhagic infarctions and interstitial hemorrhages as a forerunner of the rupture, and hemopericardium, as a consequence of it.

10. There was no evidence that subintimal hemorrhage of the coronary arteries was increased by anticoagulant therapy (9 per cent, untreated, *vs.* 6 per cent, treated).

11. Extracardiac hemorrhage was relatively uncommon in both groups. Only 17 per cent of the untreated cases and 20 per cent of the treated cases showed any extracardiac hemorrhage on gross autopsy examination. These hemorrhages involved only 2.0 per cent of the organs examined in untreated cases and 2.7 per cent of the organs examined in treated cases. Addition of microscopic hemorrhages approximately doubled these percentages, but such hemorrhages were of little import clinically.

12. In only a few cases could the foregoing hemorrhagic findings be attributed to the prolongation of prothrombin times beyond the recommended therapeutic range

Some of these foregoing differences were found statistically significant, and others were not. For those found not significant, this finding affords no positive proof of no relationship and in small samples can be seriously misleading. For those found significant, on the other hand, this significance may have resulted, in part at least, from the artificial upward bias introduced by the effect of anticoagulants on thromboembolic complications, as previously explained (see page 421). Since the extent of this bias cannot be evaluated in most types of hemorrhage, the findings on hemorrhage and rupture from a statistical angle cannot be considered definitive.

Nevertheless, since the relationships were predominantly in the direction to be expected from the physiological action of anticoagulants and since minor bleeding was also more frequent clinically in the treated than in the untreated group, the difference is probably real. *It seems safest, therefore, to base clinical practice on the expectation that anticoagulants may increase somewhat the frequency and severity of hemorrhage, particularly intracardiac hemorrhage, and may increase the risk of myocardial rupture and hemopericardium with cardiac tamponade. Alertness on the part of the clinician and good management of anticoagulant therapy can minimize these risks. Therefore the physician using anticoagulants should not only supervise such therapy with care but also should be equipped for the clinical recognition and treatment of cardiac tamponade and other hemorrhages both in and outside the heart*

Concluding Recommendations Regarding the Use of Anticoagulant Therapy in Myocardial Infarction[u]

The autopsy analysis has indicated that the clinical findings reported in previous chapters have understated both the risk of thromboembolic complications when no anticoagulants are given and the extent to which the use of anticoagulants can reduce the frequency of thromboembolic complications. The autopsy findings reinforce, therefore, rather than negate the conclusions reached from the clinical findings as to the advantages of anticoagulant therapy. On the other hand, they have also indicated that the clinical findings understated the

[u] In January, 1954, a fuller summary of the entire report was published simultaneously in *Modern Concepts of Cardiovascular Disease*,[51] in the United States and in *The Lancet*, in England[52]

Appendices

A Comparative Evaluation of Tromexan[a] and Dicumarol in the Treatment of Thromboembolic Conditions—Based on Experience with 514 Patients[b]

A REPORT OF THE COMMITTEE ON ANTICOAGULANTS OF THE AMERICAN HEART ASSOCIATION

(An evaluation of the comparative actions of Tromexan and dicumarol is herein reported. Five hundred fourteen patients were studied, a total experience of 6,642 days of Tromexan therapy and 5,006 days of dicumarol therapy were reviewed and analyzed. Previous reports of the more rapid initial prolongation of the prothrombin times and more rapid return to normal following cessation of therapy with Tromexan were confirmed. During adequate therapy the protection against thromboembolism was approximately equal for the two drugs. In other respects and with minor variations Tromexan and dicumarol were found to be quite comparable. The general advantages of anticoagulant therapy in the prevention of deaths and thromboembolic complications in myocardial infarction were confirmed.)

FOLLOWING the demonstration that anticoagulant therapy is of value in the treatment of a variety of thromboembolic disorders, investigators have sought to find more satisfactory agents than heparin and dicumarol. Pantol,[1c] phenylindanedione,[2] BL-5,[3] Tromexan[4] and, recently, Treburon[5] have been tested for clinical use. The reports in the literature regarding Tromexan appeared to justify a more comprehensive clinical trial of this drug.

The Committee on Anticoagulants of the American Heart Association has attempted to evaluate the merits of Tromexan[d] as compared with dicumarol, now in common use.[e] An attempt has been made to answer certain questions regarding: (1) the relative speeds of onset and cessation of action; (2) the toxicity of Tromexan, exclusive of hemorrhage, if any; (3) the comparative hemorrhagic tendencies of the two drugs; (4) the relat[illegible] among the participating hospitals listed in table 1. Patients with a variety of thromboembolic disorders were

Aided by grants from the American Heart Association, the Kress Foundation, the Albert and Mary Lasker Foundation, the Lillia Babbit Hyde Foundation, and the Hampil Foundation.

[a] Specific instructions for administering Tromexan will be found in Appendix D

[b] Scarrone, L. A, Beck, D. F, and Wright, I. S, reprinted from Circulation, vol VI, no. 4, October 1952.

[c] Reference numbers throughout this appendix refer to the bibliographic references on p. 491.

[d] Known as Peletan in Czechoslovakia. Tromexan is sometimes referred to as DEA, from an alternate name [illegible] acetate. T[illegible] ourtesy [illegible]

[e] The [illegible] of this A[illegible] reported on the use of dicumarol in myocardial infarction.[17] As more than 1000 patients were studied in that series, frequent references are made in this study to the results compiled in the previous work.

traindications), with subsequent doses to determined by the daily prothrombin el[f]

dy Plan and Composition of the Sample[g]

The case records for the study were lected on a cooperative basis under which ven different hospitals pooled their exrience. Of the records submitted, 514 met e criteria for acceptance for the study.[h] ese were distributed by hospitals as llows: 47 from Bellevue Hospital in New ork City, 119 from Henry Ford Hospital Detroit, 22 from Jackson Memorial Hosital in Miami, 115 from Lakeside Hospital Cleveland, 28 from the Mayo Clinic in ochester, 100 from The New York Hosital in New York City,[i] and 83 from ennsylvania Hospital in Philadelphia. Most of the hospitals included private paients as well as ward cases in their samples, ut ward cases predominated in the total.

A variety of thromboembolic diagnoses were included in the sample and no attempt was made to regulate the proportion of the total sample in each diagnostic group. For the duration of the study the cooperating hospitals undertook to treat with either Tromexan or dicumarol each patient admitted to a cooperating service and diagnosed as having a thromboembolic condition except when specific medical contraindications to the use of anticoagulants were present. Additional cases were also treated with these anticoagulants for prophylactic

tients with myocardial infarction; 87, or 17 per cent, were patients with thrombophlebitis or venous thrombosis; 41, or 8 per cent, were patients with pulmonary infarction (or pulmonary infarction combined with thrombophlebitis or venous thrombosis); 20, or 4 per cent, were patients with other arterial thrombosis or embolism (cerebral, renal, and others), and 104, or 20 per cent, were patients receiving anticoagulants as a protection against possible thromboembolic developments in coronary insufficiency,[j] postoperative states, auricular fibrillation with rheumatic heart disease, or miscellaneous conditions. The number of patients in each of these groups receiving each anticoagulant is given in table 2. The period of therapy was determined by the attending physician in each case, but records for a six-week period were requested in the instance of patients with myocardial infarction where feasible. Records beyond 42 days were not tabulated unless the patient continued in the hospital for a longer period and then only for a maximum of 92 days.

To assure nonselectivity, the hospitals were urged to use Tromexan in the treatment of patients admitted on the even days of the month and dicumarol for those admitted on odd days, or vice versa. All the cooperating hospitals except the Mayo Clinic (other programs interfered) attempted to follow this recommended procedure. Administrative errors, delays in instructions, and other difficulties prevented the plan from working out perfectly, with the result that a number of exceptions were made in

[f] Daily dosage requirements average 450 mg. to 900 mg. Some patients require only 300 mg. per day, others as much as 1200 mg The widest range in this study was 150 mg. every other day and 1650 mg. per day.

[g] To reduce the length of the report, most of the statistical tables have been omitted A supplementary set of these ...

... because of an error in diagnosis, provided the revised diagnosis involved no risk of thromboembolism sufficient to justify such therapy.

[i] Five cases treated by staff members of The New York Hospital at Doctors Hospital are included in this total.

[j] Patients originally diagnosed as probably having myocardial infarction but found later to have coronary artery disease but no infarction were included here.

treated in this series. Details of each individual case history were compiled on extensive master forms and reviewed by us. A total of 514 cases was accumulated in approximately a 12 month period and forms the basis of this report.

Historical Review of Tromexan

Tromexan is a coumarin derivative, 3,3'-carboxymethylenebis (4-hydroxycoumarin) ethyl ester (also referred to as Pelentan, BOEA and DEA). The acid form was prepared in 1940,[6] but was relatively inactive. Esterification[7] caused a marked rise in activity, and this form was extensively investigated by a number of European workers. The lethal dose for animals (mice and rabbits) was reported as approximately four to five times that of dicumarol.[8] Reinis and Kubik[9] gave human requirements as approximately four times that of dicumarol and stated maximum diminutions in prothrombin occurred within 24 hours, with recovery in 48 hours. Degradation products labeled Tromexan A and B were recovered from the urine of humans and animals and found to be relatively inactive.[10] Rapid action and reversibility in contrast to dicumarol were attested in numerous reports.[8, 9, 11, 12, 13]

In the United States, Burke and Wright,[14] Solomon,[15] and Barker[16] have reported clinical experiences with this drug. In the Burke and Wright report 112 patients with various thromboembolic diseases were treated. Their data indicated that following a single dose of from 1200 to 1800 mg the prothrombin time frequently showed an increase within 18 to 24 hours, rose to therapeutic levels in an average of 30 hours, and fell to normal levels between 48 and 60 hours. The dose required for this response varied with different individuals. Maintenance dosages averaged 600 to 900 mg. per day, either in a single dose or in divided daily doses. On the basis of these figures and further experience with Tromexan at The New York Hospital, an initial dose of 1500 or 1800 mg. was recommended to the participating hospitals (in the absence of

TABLE 1

The Committee on Anticoagulants of the American Heart Association, Participating Hospitals and Responsible Investigators*

Hospitals	*Investigators*
Bellevue Hospital, *New York*	E. Hugh Luckey, M.D.
Henry Ford Hospital, *Detroit*	F. Janney Smith, M.D
Jackson Memorial Hospital, *Miami*	E. Sterling Nichol, M D
Lakeside Hospital, *Cleveland*	Harold Feil, M.D.
Mayo Clinic, *Rochester*	Nelson W. Barker, M.D.
Pennsylvania Hospital, *Philadelphia*	Joseph B Vander Veer, M.D
The New York Hospital, *New York*	Irving S. Wright, M.D.

Consultants

Ralph S. Overman, Ph D.
Grafton E. Burke, M.D.

Central Laboratory

Irving S. Wright, M.D., *Chairman of Study*
Louis A. Scarrone, M D., *Coordinator*
Dorothy F. Beck, Ph.D., *Statistician*

* Appreciation is expressed to the residents and fellows of the various participating hospitals who have contributed their efforts towards this report, to Jane F. Jackson, M.A., for assistance with the statistical analysis, to Jean Neubauer for typing the manuscript and to the New York Heart Association for the use of its facilities.

contraindications), with subsequent doses to be determined by the daily prothrombin level.[f]

Study Plan and Composition of the Sample[g]

The case records for the study were collected on a cooperative basis under which seven different hospitals pooled their experience. Of the records submitted, 514 met the criteria for acceptance for the study.[h] These were distributed by hospitals as follows: 47 from Bellevue Hospital in New York City, 119 from Henry Ford Hospital in Detroit, 22 from Jackson Memorial Hospital in Miami, 115 from Lakeside Hospital in Cleveland, 28 from the Mayo Clinic in Rochester, 100 from The New York Hospital in New York City,[i] and 83 from Pennsylvania Hospital in Philadelphia. Most of the hospitals included private patients as well as ward cases in their samples, but ward cases predominated in the total.

A variety of thromboembolic diagnoses were included in the sample and no attempt was made to regulate the proportion of the total sample in each diagnostic group. For the duration of the study the cooperating hospitals undertook to treat with either Tromexan or dicumarol each patient admitted to a cooperating service and diagnosed as having a thromboembolic condition except when specific medical contraindications to the use of anticoagulants were present. Additional cases were also treated with these anticoagulants for prophylactic purposes at the discretion of the cooperating staff. Two hundred and sixty-two, or 51 per cent of the cases thus collected, were patients with myocardial infarction; 87, or 17 per cent, were patients with thrombophlebitis or venous thrombosis; 41, or 8 per cent, were patients with pulmonary infarction (or pulmonary infarction combined with thrombophlebitis or venous thrombosis); 20, or 4 per cent, were patients with other arterial thrombosis or embolism (cerebral, renal, and others), and 104, or 20 per cent, were patients receiving anticoagulants as a protection against possible thromboembolic developments in coronary insufficiency,[j] postoperative states, auricular fibrillation with rheumatic heart disease, or miscellaneous conditions. The number of patients in each of these groups receiving each anticoagulant is given in table 2. The period of therapy was determined by the attending physician in each case, but records for a six-week period were requested in the instance of patients with myocardial infarction where feasible. Records beyond 42 days were not tabulated unless the patient continued in the hospital for a longer period and then only for a maximum of 92 days.

To assure nonselectivity, the hospitals were urged to use Tromexan in the treatment of patients admitted on the even days of the month and dicumarol for those admitted on odd days, or vice versa. All the cooperating hospitals except the Mayo Clinic (other programs interfered) attempted to follow this recommended procedure. Administrative errors, delays in instructions, and other difficulties prevented the plan from working out perfectly, with the result that a number of exceptions were made in

[f] Daily dosage requirements average 450 mg to 900 mg. Some patients require only 300 mg. per day, others as much as 1200 mg The widest range in this study was 150 mg every other day and 1650 mg. per day.

[g] To ... [illegible]

... because of an error in diagnosis, provided the revised diagnosis involved no risk of thromboembolism sufficient to justify such therapy.

[i] Five cases treated by staff members of The New York Hospital at Doctors Hospital are included in this total.

[j] Patients originally diagnosed as probably having myocardial infarction but found later to have coronary artery disease but no infarction were included here.

the anticoagulant to which patients were assigned.[k] When assembled, the alternate series was found to consist of 355 cases, of which 160 had been treated with dicumarol, 172 with Tromexan, and 23 with both drugs.[l] Fortunately, the exceptions were made in both directions and there appeared to be no systematic basis for the shifts made except that dicumarol was selected by some physicians when long-term home therapy was contemplated. Some of the patients in the mixed drug group had been switched to dicumarol in preparation for ambulatory treatment. In other instances one anticoagulant did not give satisfactory results with a particular patient so that the other was tried. The choice of one drug in preference to the other did not appear to be associated with observable characteristics of the patients in any way that would affect the comparability of the two groups.

[k] Twenty-eight per cent of the patients that should have received dicumarol received Tromexan only or both anticoagulants and 19 per cent of those that should have received Tromexan received dicumarol only or both drugs.

[l] Patients from one cooperating service that attempted alternation unsuccessfully are included among group referred to as "special."

Since it was desirable that a larger number of cases be studied than this alternate-day procedure had procured, these cases were supplemented with 159 cases, most of which had been treated with Tromexan,[m] collected under circumstances where there had been no systematic alternation with dicumarol. These additions brought the total cases available for analysis to 514, of which 181 were dicumarol cases, 288 Tromexan cases, and 45 mixed drug cases. These cases received a total of 6,642 days of therapy with Tromexan only and 5,006 days with dicumarol only.[n]

In view of these additions and exceptions, confidence in the comparability of the two groups must rest primarily on an analysis of the types of cases included rather than on the presumed randomness of the alternation procedure. The most conspicuous difference between the dicumarol and Tromexan group is that the latter included a higher proportion of cases having a diagnosis of thrombo-

[m] Of these, 116 received Tromexan only; 21, dicumarol only; and 22, both Tromexan and dicumarol.

[n] When a case received both drugs, the days were divided between the two anticoagulants according to the actual days each was received.

TABLE 2

Number of Patients Studied and Number of Deaths, by Diagnosis and Anticoagulant Received

Diagnostic Group	Number of Patients in Sample				Number of Deaths			
	Total	Anticoagulant Used			Total	Anticoagulant Used		
		Tromexan	Dicumarol	Both Tromexan and Dicumarol		Tromexan	Dicumarol	Both Tromexan and Dicumarol
Myocardial infarction	262	139	106	17	31	15	16[a]	—
Thrombophlebitis or venous thrombosis	87	54	18	15	2	1	—	1
Pulmonary infarction[b]	41	22	17	2	4	3	1	—
Other arterial thrombosis or embolism	20	10	9	1	3	1	1	1
Coronary insufficiency and prophylactic purposes	104	63	31	10	4	4	—	—
Total sample	514	288	181	45	44	24	18	2

[a] Including two deaths in which Paritol may have contributed to death.

[b] With or without accompanying thrombophlebitis or venous thrombosis.

phlebitis.[a] When this diagnosis is omitted, the distribution of the two groups by diagnosis is similar. The excess of thrombophlebitis cases in the Tromexan group was produced by the concentration in this category of these "special" Tromexan cases (cases collected without alternation with dicumarol). Correction of the basic complication and hemorrhage rates for this difference in sampling was attempted and is reported in subsequent sections.

The Tromexan and dicumarol groups also differed with respect to the proportion of the total days of anticoagulant therapy observed that fell in the early period of the illness, particularly in the first two weeks.[b] The corrected basic rates previously mentioned also correct for this dissimilarity between the two groups, which is again due to the "special" Tromexan cases added to increase the sample since they happened to have particularly short periods of therapy. This same difference is reflected also in the total *periods* of therapy. The Tromexan group received an average of 21 days of protection with Tromexan only, that is, days without supplementation with heparin or Paritol, and the dicumarol group, 24 days with dicumarol only. Tromexan cases were observed for a total of 34 days on the average and dicumarol cases for an average of 37 days.

A third difference occurred in a minor degree with respect to supplementation with other [illegible] ...ntation with heparin was the same in the two groups, 21 per cent of the cases in each group receiving supplementation with heparin for an average of slightly less than three days for each case with supplementation. However, 17 per cent of the dicumarol group and only 8 per cent of the Tromexan group received Paritol, for averages of three and two days respectively. Comparisons between the drugs are protected from the influence of this extraneous factor by the use of day rates that exclude all periods of supplementation.

On the test of severity of onset of the illness the samples favor Tromexan slightly, for 23 per cent of the dicumarol cases as compared with 18 per cent of the Tromexan cases were considered severe at onset by the reporting physician.[c] The difference is due again to the addition of the "special" Tromexan cases, an unduly large number of which were mild at onset. Since a precise definition of "severe at onset" is difficult and the difference is small, corrections for this factor were not attempted. If corrections had been made, they might have increased slightly the thromboembolic complication rate for Tromexan.

Because of the small numbers in some diagnostic subgroups, corrections for age and sex differences also were not feasible. Fortunately, differences in age were slight. Forty-six per cent of the Tromexan cases were 60 years of age or older but only 38 per cent of the dicumarol cases; however, the age averages for the two groups were closely similar, 56 years and 55 years respectively. Since no clearly significant relationship between age and complications and hemorrhages was found in the dicumarol study,[11] it may be assumed that these differences do not affect the comparisons between the two anticoagulants. In sex composition the two groups could hardly have been more closely similar, for 65 per cent of each were males and 35 per cent females. Not all diagnostic subgroups were thus alike in age and sex composition and other characteristics compared, but in general the

[a] Nine per cent [illegible] ... respectively.

[c] The correction for sampling differences in diagnosis undertaken at various points does not correct for this difference.

larger and more homogeneous groups showed reasonable similarity.[r]

Analysis of the previous medical history of the two groups, particularly with respect to the presence of previous episodes of bleeding or thromboembolic episodes, was not feasible within the time limits, but the intensive review of the records involved in the complication and hemorrhage analysis did not leave the impression that any obvious selection or bias occurred in this respect and there is no logical reason to expect selection.

In general, it may be concluded that while differences between the two samples did occur with respect to diagnosis, period of therapy, and severity, these differences cannot be considered the explanation for the differences between the two drugs reported, for corrections have been made for two of the three differences and the third is such as would probably increase slightly rather than reduce the reported differences. Where conclusions are believed affected by sampling differences, qualifying statements have been appended.

Prothrombin Time Reporting

Local differences in technics for performing prothrombin time tests constitute another possible source of error in comparisons between two anticoagulants when the basic data are obtained from more than one hospital. To overcome this difficulty, insofar as possible, the percentages of prothrombin activity approximately equivalent to all prothrombin times reported in seconds by the cooperating hospitals were first determined on the basis of dilution curves for normal blood submitted by the hospitals concerned. These percentages were then converted back into seconds, this time with a standardized meaning, by means of the composite prothrombin time curve developed for purposes of the dicumarol study.[s] Table 3, developed for use in this conversion procedure, indicates the standardized meanings (in terms of percentages of prothrombin activity) of 17, 25 to 39, 50 to 59 and 60 seconds or more as used in the text.

This table illustrates dramatically the great divergencies in the meaning of prothrombin times in seconds from hospital to hospital.[t] For example, 60 seconds, meaning in this study 6 per cent, was approximately equivalent at the time of the study to 49 seconds at Bellevue and 96 seconds at the Mayo Clinic. Similar differences occurred with respect to the meaning of the "therapeutic range" within which physicians cooperating with the project were advised to keep prothrombin times. On the basis of the findings of the previous dicumarol study,[u] this range was defined as 25 to 39 seconds on the composite curve or 23 to 11 per cent in terms of prothrombin activity.[s] The approximate equivalent of this range at Bellevue was 22 to 33 seconds and at the

[r] The sex difference for myocardial infarction cases is an exception to this statement for 82 per cent of the Tromexan group in this category were males as compared with 70 per cent of the dicumarol cases. This difference probably did not affect the conclusions since in the previous dicu-
...al study no statistically significant difference
incidence of

[s] This curve was based on the medians of findings for various dilutions for normal blood samples tested by the cooperating hospitals using the Link-Shapiro modification of the Quick method.

[t] The use of percentage will not improve this situation in a given hospital unless the control and each reading are first carefully determined in seconds Errors in this determination will be perpetuated when converted into percentage which is essential only for comparison with other laboratories.

[u] The recommendation was based on the findings with respect to the incidence of thromboembolic complications and hemorrhages per 1000 days of dicumarol therapy at different prothrombin time levels. It was found that prolongation beyond 25 seconds was necessary to afford the patient maximum protection against thromboembolic complications, but that prolongation beyond 40 seconds afforded no increased protection. Since the risk of hemorrhage was found to increase rapidly above 40 seconds, 40 seconds was defined as the upper limit of the therapeutic range

Mayo Clinic, 32 to 56 seconds. If the impli-tions of the present findings are not to be issed or misinterpreted, each reader will ed to translate the seconds as reported this article into their equivalent for the boratory with which he deals. This can be one by comparing the dilution curves run r normal blood at various control times y his laboratory with the percentages re-orted on line two in the foregoing table.

Effects on the Prothrombin Time

Previous experience, as mentioned before, as shown that Tromexan acts with greater apidity than dicumarol, and that its effect s more rapidly dissipated after cessation of herapy. These findings were confirmed in he present study. Patients followed at The New York Hospital (where the time of the nitial dose was definitely known) may be ised to illustrate the difference in response pattern. Of 26 patients receiving either 1500 or 1800 mg. of Tromexan on the first day, 12 (or 46 per cent) rose above 20 seconds in 24 hours and 24 (or 92 per cent) rose above 20 seconds by 48 hours. Of 23 cases receiving 300 mg. of dicumarol on the initial day only six (or 26 per cent) were above 20 seconds in 24 hours and only 14 (or 61 per cent) had risen above this level in 24 hours.* Patients who were in shock or manifested hepatic or renal dysfunction were excluded from both groups. In the Tromexan group only patients who received either 1500 or 1800 mg. of the drug were included, as an initial dose of 1200 mg. was frequently insufficient to effect a good prothrombin response. Work performed at Bellevue Hospital by Dr. Erwin Nydick (unpublished) indicated that single doses of 1500 mg. and 1800 mg. of Tromexan (given to patients with non-thromboembolic illnesses) showed a wide range of response in prothrombin times. Wide variation in responses to a single dose of dicumarol have been frequently encountered and reported.[19] This variability serves to emphasize the fact that dosage requirements of either drug must be based on consecutive prothrombin readings.

On the other hand, the fall in the prothrombin time toward normal after cessation of Tromexan is notably more rapid and

* For graphic presentation of these cases see figure 16 in reference 20.

TABLE 3

Number of Seconds for Each Cooperating Hospital Approximately Equivalent on the Average at the Time of the Study to Given Seconds on the Composite Curve Developed Previously for Use in the Dicumarol Study

In seconds	*Composite Curve*			
	17 (upper limit of normal)	25–33 ("therapeutic range")	50–59	60 or more
In per cent prothrombin activity	58% or more	23%–11%	7%–6(.3)%	6(.2)% and under
Average Equivalents in Seconds in Laboratories of Cooperating Hospitals*				
Bellevue, *N. Y*	15	22–33	42–48	49 or more
Henry Ford, *Detroit*	17	24–37	50–54	55 or more
Jackson Memorial, *Miami*	16	24–40	51–59	60 or more
Lakeside, *Cleveland*	18	31–68	90–97	98 or more
Mayo, *Rochester*	21	32–56	86–95	96 or more
The New York Hospital, *N Y*				
General laboratory	18	27–43	59–74	75 or more
Research laboratory	16	26–43	56–67	68 or more
Pennsylvania, *Philadelphia*	18	31–50	60–64	65 or more

* Computed from dilution curves for normal blood furnished by hospitals.

predictable than after dicumarol. Not infrequently the prothrombin time has been noted to continue rising after dicumarol is stopped whereas this was rarely observed following discontinuance of Tromexan. In this series of 263 instances tabulated in sequence where Tromexan was omitted for one day, the prothrombin time showed a definite decrease in all cases but 17 on the following day. Of these 17, five were unchanged, and in 12 the prothrombin time rose. In two of these rises the increase was slight. Five of the 12 cases had received unusually large doses, two had renal disease, one was hypersensitive to small doses, and in two the rises remained unexplained. In a similar setting of 113 cases of dicumarol cessation, the prothrombin time fell in 70, remained the same in four, and rose in 30 (of which one case had mild renal disease, and one had hepatomegaly, the remaining being unexplained). These findings illustrate the dependability with which the effect of Tromexan diminishes over a 36 hour period, but in uncommon instances some elevation of the prothrombin time may persist for a number of days. There were at least four instances in this series of elevations above 40 seconds that stayed above this level three to five days without further Tromexan. Three showed mild renal disease and one of these congestive hepatomegaly. Data for the evaluation of the fourth were lacking. This phenomenon is not uncommon in the case of dicumarol and no attempt was made to analyze data on its frequency.

As a further test of the speed of drop with Tromexan, all instances when prothrombin times reached or exceeded 60 seconds on the composite curve (6 per cent or less) under both Tromexan and dicumarol were noted. In those instances in which the patient was not influenced by heparin or Paritol, received no anticoagulant on the first day at 60 seconds, and was not treated with vitamin K or blood, the times the first day after this first reading of 60 seconds or more were tabulated. Sixty-one such qualifying instances were found during Tromexan therapy but only 11 during dicumarol therapy. On the day following the first observation of these excessive prolongations, 30 or half of the 61 Tromexan cases showed times below 25 seconds, and 52 of the 61 had dropped to below 40 seconds or out of the zone of excessive hemorrhage risk. Only four remained above 60 seconds. In contrast, 6 of the 11 available dicumarol cases remained above 60 seconds the day following under similar circumstances, and none had dropped below 25 seconds. While this dicumarol sample is much too small, the findings are consistent with clinical experience with this drug and may be assumed representative. Anticoagulant therapy must take into account this great difference in the probable prothrombin level the day following excessively prolonged times.

The time of return of the prothrombin time to normal levels after complete cessation of therapy was determined by daily prothrombin times in 51 of the Tromexan cases whose time on the day of the last dose was in the "therapeutic range" (between 25 and 39 seconds, or 23 per cent to 11 per cent). Corresponding data were available for only 11 of the dicumarol cases. (Prothrombin readings for most patients were terminated before the base line was reached.) All but 11 of the 51 Tromexan cases with usable records showed normal times (17 seconds, or 58 per cent or more) by the third day after the last dose, the maximum time for the return being six days and the average two and nine-tenths days. The corresponding average for the 11 dicumarol cases was five and one-tenth days and the maximum, eight days. This average figure compares well with the four and seven-tenth average number of days to normal for the study of dicumarol in myocardial infarction based on 78 cases with records to normal and times between 20 and 39 seconds on the day of the last dose. In this former study with dicumarol the maximum time for the return was 13 days instead of eight.[18] In view of the

rapidity of the fall with Tromexan from high levels, the failure of Tromexan cases to return immediately to normal may seem surprising, but it is common experience that the prothrombin time may linger a few seconds above the base line for some time after a previously rapid fall. This may actually be protective rather than undesirable.

Lability of prothrombin times in Tromexan treated patients was noted in a number of the case reports submitted to us. Barker[18] and Wright[19] have commented upon this in the literature. This lability is seen in the sudden unpredictable rises in the prothrombin time that occasionally occur during an apparently stabilized regimen. Figure 1 illustrates a case in which satisfactory control was consistently maintained and figure 2 illustrates a case in which such an "escape" occurred. In the latter case, as in most such instances, immediate cessation of therapy at that point resulted in a rapid regression of the prothrombin time.

In connection with lability studies, all rises above 60 seconds were counted. A total of 105 rises above 60 seconds occurred during therapy with Tromexan only among 333 patients receiving Tromexan at some time and 25 during therapy with dicumarol only among 226 patients receiving dicumarol at some time (mixed drug cases counted under both drugs). Forty-four per cent of the dicumarol rises were treated with vitamin K or blood, but only 14 per cent of the Tromexan rises received similar treatment. A total of 118 days under Tromexan only and 42 days under dicumarol only were known to be at 60 seconds or over. Thus on the average the times remained 60 seconds or

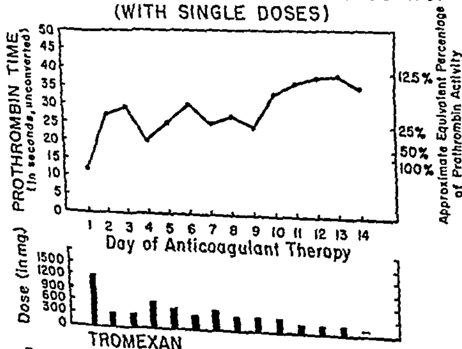


Figure 1. Case illustrating good control of prothrombin times after rapid prolongation following a small initial dose of Tromexan given for acute thrombophlebitis. (Note slight fluctuations in daily prothrombin times. Drug was administered in a single daily dose)

predictable than after dicumarol. Not infrequently the prothrombin time has been noted to continue rising after dicumarol is stopped whereas this was rarely observed following discontinuance of Tromexan. In this series of 263 instances tabulated in sequence where Tromexan was omitted for one day, the prothrombin time showed a definite decrease in all cases but 17 on the following day. Of these 17, five were unchanged, and in 12 the prothrombin time rose. In two of these rises the increase was slight. Five of the 12 cases had received unusually large doses, two had renal disease, one was hypersensitive to small doses, and in two the rises remained unexplained. In a similar setting of 113 cases of dicumarol cessation, the prothrombin time fell in 70, remained the same in four, and rose in 30 (of which one case had mild renal disease, and one had hepatomegaly, the remaining being unexplained). These findings illustrate the dependability with which the effect of Tromexan diminishes over a 36 hour period, but in uncommon instances some elevation of the prothrombin time may persist for a number of days. There were at least four instances in this series of elevations above 40 seconds that stayed above this level three to five days without further Tromexan. Three showed mild renal disease and one of these congestive hepatomegaly. Data for the evaluation of the fourth were lacking. This phenomenon is not uncommon in the case of dicumarol and no attempt was made to analyze data on its frequency.

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period. No differences appeared in respect to the avoidance of dangerous prothrombin times in the two periods. However, when the Tromexan cases were analyzed according to whether they received single or divided daily doses of Tromexan, the results were more striking. They are shown graphically in figure 3. Patients maintained largely[x] on single daily doses had 3 6 per cent of their times at 50 seconds or more; patients on a mixed regimen, 2.6 per cent of their times these elevations; and patients largely divided doses, only 0 4 per cent of their nes in this range. In this last group actually ly one reading exceeded 49 seconds—a re-

patients largely on divided doses were a very small group and received only 253 days of Tromexan therapy, with the result that the finding of improved stability cannot be considered conclusive at this time. Most of the patients receiving dicumarol were treated only with single daily doses. The record for such patients showed that 1.8 per cent of their times were in this range, a record midway between the single and divided dose rates for Tromexan. The results, if confirmed by further clinical experience, suggest that Tromexan therapy using divided daily doses may offer to the practitioner the advantages of the quick rise and fall characteristics of Tromexan without its disadvantage of uncontrolla-

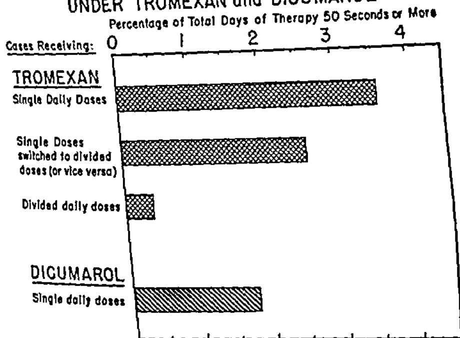


Figure 3. Percentage of total days spent under the influence of Tromexan and dicumarol only and having usable prothrombin times of 50 seconds or more (7 per cent or less) among patients receiving Tromexan in single and/or divided daily doses and among patients receiving dicumarol in single daily doses.

over one and one-tenth days under Tromexan and one and seven-tenth days under dicumarol. The contrast would probably be greater except for the more intensive therapy of the dicumarol "escapes."

Since these undue elevations constitute a potential hemorrhagic hazard to the patient, the comparative incidence of all elevations above 50 seconds in the two anticoagulants also was studied. Before tabulation, prothrombin times were converted to a comparable basis and days under two anticoagulants at the same time and the first day of therapy were omitted. Under both drugs the proportion of prothrombin times of 50 seconds or more was slight. Of 3,927 days of therapy with dicumarol only and having usable prothrombin times, 1.9 per cent were 50 seconds or more (7 per cent or less), whereas, of 5,965 similar days on Tromexan only, 3.3 per cent were 50 seconds or more.*

Because it was thought that increasing experience with Tromexan might lead to a decrease in the number of these elevations, the Tromexan sample for each hospital was divided chronologically into cases treated during the first and second half of the study

* The data refer to total days at 50 seconds or more, not to the number of separate rises. In the case of Tromexan high times fall rapidly again to lower levels, as previously demonstrated, whereas in the case of dicumarol, they tend to persist several days. Consequently, the larger number of separate instances of rises that occurred in the case of Tromexan were partially counteracted in the above rates by their shorter duration

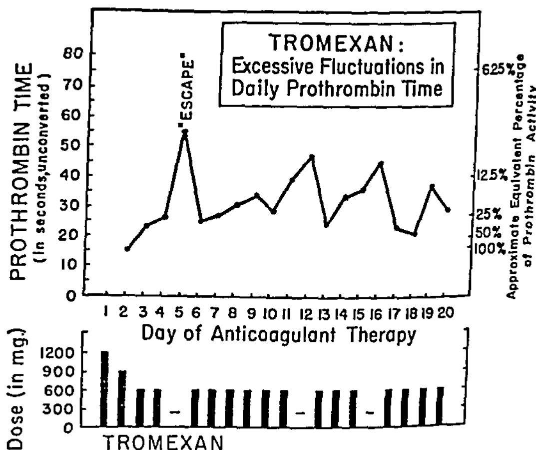


Figure 2. Case demonstrating sudden changes in prothrombin times with single doses in a patient receiving Tromexan for acute thrombophlebitis. [Cessation of drug for one day resulted in prompt fall in the next prothrombin time. Note lack of response to small (1200 mg.) initial dose.]

drugs would appear to be about equally effective as prophylaxis against thromboembolic complications, at least in this condition. The myocardial infarction rates are also low in a comparative sense since they are about one-third below the corresponding rate of 3.1 per 1000 days of therapy for the treated group in the earlier study of dicumarol therapy in coronary thrombosis with myocardial infarction[18] and far below the corresponding rate of 12.6 for the control group in that series for days of their illness corresponding to the period of therapy for the treated group. In this former study, many physicians were using dicumarol for the first time and hesitated to administer adequate doses, with the result that prothrombin times were too low for adequate protection in a substantial proportion of cases.

For the other diagnostic groups shown in figure 4, lack of close comparability in components and small numbers handicap conclusions. Pulmonary infarction was combined with thrombophlebitis and venous thrombosis because of the frequency with which they were found together in a double diagnosis. The rates of thromboembolic complications for both Tromexan and dicumarol for this group were similar but relatively high, 8.1 and 8.8 per 1000 days, respectively, after correction for the major sampling differences.[dd] In general, thrombo-

[dd] The corresponding uncorrected rates were 8.6 for Tromexan and 8.3 for dicumarol. These uncorrected rates include one cancer case that developed three complications under dicumarol and

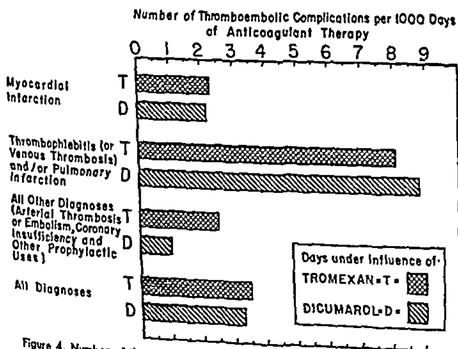


Figure 4. Number of thromboembolic complications of all types occurring on days when patients were under the influence of Tromexan or dicumarol only per 1000 days of corresponding type of anticoagulant therapy, by diagnosis (corrected rates).

bility. Further trial with divided doses is indicated.

Thromboembolic Complications

The cooperating hospitals were asked to watch carefully for, and to report in detail, all thromboembolic complications occurring both in and outside the heart during the period of observation for each case. After a critical review, such thromboembolic complications as had been diagnosed on the basis of clinical evidence, signs, or symptoms as definite or probable were included in the counts. Those appearing improbable on such a basis and those undiagnosed until autopsy studies revealed them were excluded since protocols were available for only a small proportion (3 per cent) of the total cases.

By these criteria, a total of 59 thromboembolic complications occurred during the period of observation. Of these, one occurred before therapy could be instituted,[y] and 17, after the termination of anticoagulant therapy. The latter will be discussed separately. No complication occurred on days when patients were protected by heparin or Paritol. One complication, a myocardial infarction, occurring when the patient was influenced by both Tromexan and dicumarol, cannot be allocated to either anticoagulant and is therefore omitted from all further counts. The other 40 complications occurred during either dicumarol or Tromexan therapy and will be discussed in detail.

The total counts converted to a day rate basis[z] are shown in figure 4. On the 6,642 days when patients were under the influence of Tromexan as the only anticoagulant, a total of 25 thromboembolic complications occurred, a rate of 3.8 per 1000 days of therapy. On the 5,006 days when dicumarol was the only anticoagulant, a total of 15 complications occurred, a rate of 3.0 per 1000 days of therapy.[aa] The rates are surprisingly close considering the variety of component diagnoses included and the number of other uncontrolled variables.

In order to ascertain the effects on these total rates of certain differences in the Tromexan and dicumarol samples previously noted, statistical corrections were made in these foregoing thromboembolic rates both for the larger proportion of thrombophlebitis cases and for the larger proportion of therapy in the early weeks characterizing the Tromexan group.[bb] These corrections brought the total complications during Tromexan therapy to 3.5 and the dicumarol rate to 3.3 per 1000 days. The remaining difference of 0.2 complications per 1000 days of therapy cannot be considered significant either statistically or medically.

For myocardial infarction cases, the most homogeneous diagnostic group in the sample, the day rates for the two anticoagulants after similar corrections for sampling differences were almost identical, namely 2.3 thromboembolic complications per 1000 days of Tromexan therapy as compared with 2.2 per 1000 days for dicumarol therapy (see figure 4).[cc] While this very close similarity is no doubt a chance coincidence, the two

[y] Since cases were classified by the thromboembolic condition for which anticoagulants were first prescribed, there was little opportunity for complications prior to anticoagulant therapy.

[z] Day rate here refers to number of complications per 1000 days of Tromexan and dicumarol therapy.

[aa] When the "special" (nonalternate) cases are excluded, the rate for the alternate series during Tromexan therapy becomes 4.2 and that during dicumarol therapy becomes 3.5 per 1000 days while the rate during Tromexan therapy for the "special" Tromexan series is changed to 3.1.

[bb] The method of correction used involved retaining the specific rates by week of illness and diagnostic groups actually found for dicumarol and Tromexan, but giving these specific rates the same proportionate weights in the total rate for each anticoagulant. The procedure is similar to that used in the computation of standardized birth and death rates. The weights used were based on the distribution of the total sample days of therapy for both anticoagulants.

[cc] The corresponding uncorrected rates were 2.2 per 1000 for Tromexan and 2.2 per 1000 days for dicumarol.

drugs would appear to be about equally effective as prophylaxis against thromboembolic complications, at least in this condition. The myocardial infarction rates are also low in a comparative sense since they are about one-third below the corresponding rate of 3.1 per 1000 days of therapy for the treated group in the earlier study of dicumarol therapy in coronary thrombosis with myocardial infarction[13] and far below the corresponding rate of 12.6 for the control group in that series for days of their illness corresponding to the period of therapy for the treated group. In this former study, many physicians were using dicumarol for the first time and hesitated to administer adequate doses, with the result that prothrombin times were too low for adequate protection in a substantial proportion of cases.

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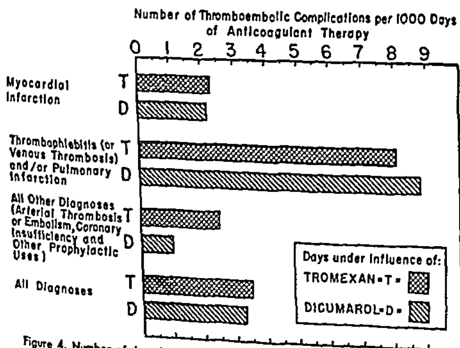


Figure 4. Number of thromboembolic complications of all types occurring on days when patients were under the influence of Tromexan or dicumarol only per 1000 days of corresponding type of anticoagulant therapy, by diagnosis (corrected rates).

phlebitis in patients receiving adequate Tromexan therapy appeared to resolve as rapidly and with as few sequelae as those treated with dicumarol.

The remaining group consists largely of patients with whom anticoagulant therapy was used for prophylactic purposes, especially with evidence of coronary insufficiency, with suspected but not clear-cut attacks of coronary thrombosis, and postoperatively. Included are also a few cases of arterial embolism and one of cerebral thrombosis. The incidence of complications in these cases was exceedingly low, the corrected rates being only 2.5 complications for Tromexan and 1.0 for dicumarol per 1000 days of therapy.** In this group, as in the total sample, the rate of complications with Tromexan is slightly higher than the rate with dicumarol, but comparability between these varied groups is not fully assured and chance factors may well account for such slight differences. In addition, a problem of control under Tromexan entered in which will be discussed later.

Because of the varying duration and timing of anticoagulant therapy from case to case and the varied extent of supplementation with heparin or Paritol, cases are not strictly comparable with one another. Therefore, rates have been based on days of anticoagulant therapy rather than on case counts, a type of rate doubtless new to some readers. In visualizing the meaning of these rates, the physician is justified in thinking of 1000 days as approximately equivalent to 50 cases treated with anticoagulants for 20 days each, a typical period of therapy. On this basis the above rate of 2.2 complications per 1000 days under anticoagulants for the myocardial infarction group may be thought of as roughly equivalent to four or five complications *during therapy* per 100 cases treated for about three weeks each, or one to each 20 cases so treated. This rate is obviously lower than the rate of 8.5 complications per 100 cases which occurred during anticoagulant therapy in the treated group of the earlier study of the Committee,[11] and 34.9 complications per 100 cases occurring in the untreated group during a comparable period of their illness.[11] These rates omit the usual quota of complications before and after anticoagulants included in some figures in other studies.

In order to think directly in terms of patients or case rates in the present study, one must omit the 45 patients who received both Tromexan and dicumarol (referred to as the "mixed drug" cases and included in figure 4), together with 11 complications occurring in these cases. With these omissions, the complications occurring under dicumarol only were distributed by diagnosis as follows: seven complications (or 6.6 per 100) in the 106 cases of myocardial infarction and four (or 11.4 per 100) in the 35 cases of pulmonary infarction and/or thrombophlebitis or venous thrombosis. No cases receiving dicumarol only in any other diagnosis developed any complication. The complications under Tromexan were as follows: nine complications (or 6.5 per 100) in the 139 myocardial infarction cases treated with Tromexan, seven (or 9.2 per 100) in the 76 pulmonary infarction and/or thrombophlebitis or venous thrombosis cases, and two (or 2.7 per 100) in the 73 cases in the "all other" diagnoses group. Since the periods of therapy were not standardized for the two drugs, the case counts cited are not

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three under Tromexan. If this extreme case is omitted, the rates become 6.7 complications for Tromexan and 4.9 for dicumarol per 1000 days of therapy.

** The corresponding uncorrected rates were 2.7 for Tromexan and 1.0 for dicumarol per 1000 days.

[11] A rate that is strictly comparable cannot be computed for this previous study since, in the original dicumarol study, cases received an average of 28 days instead of 20 days of therapy with dicumarol only. Strictly comparable figures for the original dicumarol study would be slightly lower, perhaps 7.5 instead of 8.5 for the treated group

believed in this situation to be a fully definitive basis for the evaluation of the protective capacity of the two anticoagulants.[44]

A wide variety of thromboembolic complications both inside and outside the heart have been included in the reported totals. Specific rates by type of complication are not justified because of the low counts, but a listing will illustrate the types included. On the 5,006 days when dicumarol was the only anticoagulant in effect, the following types of complications occurred: one new myocardial infarct, two extensions of myocardial infarcts, five pulmonary infarcts (or emboli), six new episodes or recurrences of thrombophlebitis, and one embolus to the juncture of the left femoral and profunda femoral artery. On the 6,642 days when Tromexan was the only anticoagulant in effect, the complications occurring were as follows: three extensions of myocardial infarctions, five pulmonary infarcts (or emboli), 11 new episodes or recurrences of thrombophlebitis, four cerebral emboli, one renal embolus, and one extension of a cerebral arterial thrombosis.[45] In view of the small numbers and variations in the previous history of the patients, differences in the distribution cannot be attributed to the type of anticoagulant employed.

Analyses by such factors as age and sex were precluded by the small numbers within most diagnostic subgroups, but a breakdown was attempted by time of occurrence in relation to the date of onset of the original thromboembolic conditions for which anticoagulants were given. The results are reported in figure 5. In all the diagnostic groups the incidence of thromboembolic complications under therapy was highest during the first two weeks of therapy. In the myocardial infarction group Tromexan and dicumarol showed rates per 1000 days of therapy of 3.0 and 4.9 respectively during the first two weeks after the attack. During the third and fourth weeks the Tromexan and dicumarol rates were 1.8 and 1.6 per 1000 respectively. These rates compare closely with the experience in the dicumarol study,[18] for which the corresponding rate for the first two weeks was 4.5 complications per 1000 days of dicumarol therapy and 2.1 for the third and fourth week.

Since the maximum risk of thromboembolic complications clearly falls in the first and second week after the onset of the original thromboembolic condition, the more rapid initial prolongation of prothrombin time possible with Tromexan probably has distinct medical value. Unfortunately, a statistical evaluation of the reduction in risk of thromboembolism during the first three or four days of anticoagulant therapy was not feasible because a large proportion of the cases (32 per cent) received supplemental protection with heparin or Paritol, primarily in this early period. This was a sufficient proportion to blur recognition of differences between the drugs during this early period, particularly since 37 per cent of the dicumarol cases but only 28 per cent of the Tromexan cases received such supplementation. In spite of this lesser supplementation, however, the complication record for Tromexan during the first two weeks in myocardial infarction cases, as shown in figure 5, is somewhat better than the dicumarol record when supplementation days are excluded, while in the third and fourth week the rates for the two are about the same. Without more rigid controls and a larger number of cases, it is impossible to be certain whether this difference results from the more immediate protection afforded by Tromexan or some extraneous factor, but the difference is suggestive of the advantages of a rapid rise at the outset of therapy.

When the onset of the thromboembolic complications was correlated with the pro-

[44] The periods of observation and degree of supplementation also were not standardized, it being the intention to leave the hospitals complete freedom in these respects. The groups also are small and not fully homogeneous.

[45] The foregoing counts include mixed drug cases.

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By this same three-day sequence test, however, there were six "failures of anticoagulant therapy" in the case of dicumarol, one of which again was a cancer case.[kk] Omitting complications in cancer cases, the total for the entire series becomes five "true failures," a small number indeed for thromboembolic complications in about 12,000 days of anticoagulant therapy.[11]

Not included in the foregoing counts were 17 thromboembolic episodes occurring after anticoagulants were terminated, of which 15 occurred within 16 days or less of the end of anticoagulant therapy. The interim between anticoagulant and complication was deemed the number of days after the prothrombin time had returned to normal or, if these were not given, as starting after an arbitrarily chosen number of days of residual anticoagulant effect (four days for dicumarol and one day for Tromexan). This interval is of particular interest. Six complications followed a last dose of dicumarol by 3, 6, 7, 8, 9 and 16 days *after* the end of anticoagulant influence. The other nine followed a last dose of Tromexan by 2, 2, 2, 4, 6, 6, 7, 8 and 15 days after the actual or estimated end of influence. Inspection of the duration of therapy indicates that at least six of these cases had been treated for an inadequate length of time and that *therefore* some recurrence could be anticipated. Nevertheless, these complications *fall* within rather distinct time periods for each anticoagulant. The omission of the 15 and 16 day episodes leaves a range for dicumarol from three to nine days and an average of seven days and a range for Tromexan of two to eight and an average of five days, a difference that is consistent with the nature of the two anticoagulants.[mm] Thromboembolism after such intervals is not too infrequent a phenomenon. It has been suggested that this may be due to a "rebound" phase of hyperprothrombinemia or hypercoagulability, although this has not been proven in vitro. The shorter interim for Tromexan and the larger for dicumarol may suggest such a possibility. At least as likely is the possibility that the underlying disease process had not sub- [illegible]

terminating therapy anticoagulant doses should be tapered off gradually but the value of this has not been critically established. Since these recurrences and other thromboembolic complications are especially apt to occur after short courses of anticoagulant therapy, anticoagulants should certainly be continued until the risk of recurrence of thromboembolic episodes is minimal.

Hemorrhages during Anticoagulant Therapy

Hemorrhage, an extension of the therapeutic effects of anticoagulants, *represents* the limiting factor in the clinical use of these drugs. Other factors being equal, *the incidence* of bleeding in any large series under an anticoagulant reflects the controllability over the agent, as excessive prolongations of the clotting process result in a *marked* increase in the incidence of bleeding. (In small series of patients the variables are so great as to render any conclusions invalid.)

Data concerning hemorrhages in this series

[kk] One complication under Tromexan and two under dicumarol lacked times for one of the two preceding days and therefore could not be classified

[11] Conclusions regarding the relative incidence of "true failures" under the two anticoagulants should be withheld because (1) the definition of a failure is arbitrary, (2) failures diagnosed only at autopsy are omitted, and (3) the number of readings below 25 seconds and the number in the therapeutic range were not tabulated.

[mm] When one considers that the scattered residual effects of Tromexan persist from 1–6 days and those of dicumarol, 1–13 days and that arbitrary estimates of 1 and 4 days were usually used in computing the above intervals, it is quite possible that most of these complications actually occurred almost immediately after the termination of anticoagulant influence rather than after an interim period.

thrombin times at the time of the episode, it was found that only 3 of the 12 complications under dicumarol with times available for the day of onset[‖] occurred with prothrombin times below 25 seconds (24 per cent or above) on the day of the complication. On the other hand, 16 of the 22 complications in the Tromexan group with times for the day of onset had levels below 25 seconds on that day. This contrast suggests that the slightly higher incidence of complications for some diagnoses under Tromexan was related to the difficulty of controlling prothrombin levels with this anticoagulant and not to any intrinsic failure of Tromexan to prevent thrombosis at adequate prothrombin levels. This experience dramatizes the need for close watchfulness against rapid drops during Tromexan therapy.

Of the six cases in the Tromexan group with thromboembolic complications developing at prothrombin times of 25 seconds or above, only one occurred when the prothrombin time also had been maintained at a level of 25 seconds or more for the two preceding days. This one "true failure" of Tromexan therapy[‖] consisted of the recurrence and progression of thrombophlebitis in the presence of carcinomatosis—a well-known cause for failure of anticoagulants to inhibit thromboembolic complications[22,23]

‖ Times for the day of onset for three complications under dicumarol and three under Tromexan were not reported.

‖ Failure in the sense that the prothrombin time was completely within the therapeutic range during a period when a fresh thrombus could probably form.

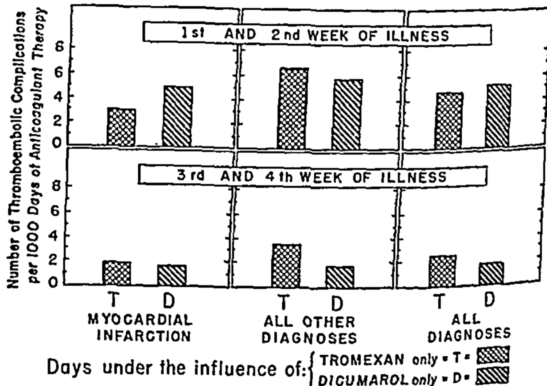


Figure 5. Number of thromboembolic complications of all types occurring on days when patients were under the influence of Tromexan or dicumarol only per 1000 days of corresponding type of anticoagulant therapy, by diagnosis and week of illness (cases with unknown date of onset and therapy after the fourth week omitted).

appeared aggravated by, precipitated by, or prolonged by, anticoagulant therapy were classified as "aggravated by anticoagulants." The resulting rates, based on 6,642 days of therapy with Tromexan only and 5,006 days of dicumarol only, showed the rate for gross hemorrhages due to anticoagulants to be 2.3 per 1000 days for Tromexan and 1.8 per 1000 days for dicumarol. Episodes aggravated by anticoagulants showed a rate of 2.4 gross bleeding episodes per 1000 days for Tromexan and of 1.2 similar episodes per 1000 for dicumarol. The total for Tromexan for gross episodes related to anticoagulants is therefore 4.7 per 1000 days and that for dicumarol, 3.0 per 1000 days.[aa] The difference in each case is small, amounting to less than 2 episodes per 1000 days of anticoagulant therapy, or approximately 3 to 4 additional episodes per 100 patients treated for 20 days each. Evaluation of this small difference is difficult.

As a first step in appraisal, statistical corrections for certain known differences between the two samples were undertaken for hemorrhage rates in the same manner previously described for thromboembolic complication rates.[oo] It was found that these corrections made only very minor changes in the rates quoted [pp] The rate for gross hemorrhages related to Tromexan was raised from 4.7 to 4.8 per 1000 days while the gross rate for dicumarol remained unchanged. Other changes were similarly small. Clearly those obvious sampling differences for which corrections were feasible do not account for the differences noted.

A further test indicated that the difference also was not produced by the addition to the sample of the Tromexan cases collected without alternation with dicumarol since the amount of the difference remained about the same when these "special" (nonalternate) cases were excluded.[qq]

Whether the difference in corrected rates for gross hemorrhages related to the two anticoagulants of 1.8 per 1000 days was due to chance was also tested. The probabilities were found to favor explanation in terms other than chance,[rr] but explanation on a chance basis could not be ruled out with the degree of certainty that is conventionally implied by the term "statistically sig-

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[aa] For comparison of rates with the dicumarol study, microscopic hemorrhages must also be included and original diagnoses other than myocardial infarction omitted When this is done, the Tromexan rate becomes 6 7 and the dicumarol rate becomes 6.3 per 1000 days of anticoagulant therapy Both these rates are about double the comparable rate of 3.3 hemorrhages per 1000 days of anticoagulant therapy in the original dicumarol study The higher rate probably reflects primarily the higher prothrombin times maintained in the present study and secondarily, perhaps, better reporting of hemorrhages

[oo] See footnote bb, p. 470 for explanation of the method employed

[pp] The process of correction left the microscopic hemorrhage rate for Tromexan unchanged (2 4 per 1000 days) and changed the dicumarol rate from 3.2 to 3.3 per 1000 days The total rate for Tromexan (gross plus microscopic) became 7.2 instead of 7.1 per 1000 and the total rate for dicumarol, 6.3 instead of 6 2 per 1000. All rates refer to hemorrhages due to, aggravated by, or pre- [illegible] days of therapy with Tromexan [illegible] be 5. [illegible] be 3 [illegible] show [illegible] marol cases in the nonalternate group showed no gross hemorrhage but the rate is meaningless in this case because of the small number in the group.

[rr] The chances were found to be about 9 per 100 that a difference equal to the difference (as corrected below) and in this direction would occur on a chance basis To apply the test it was necessary for statistical reasons to convert the corrected rates into a true proportion (the proportion of total days of therapy on which hemorrhages began) by deducting for two or more hemorrhages beginning on the same day. This procedure [illegible] same patient, whereas there was no more than one gross hemor-

were obtained by compiling descriptions of hemorrhages clinically observed and the analysis of laboratory data on microscopic hematuria and melena. Hemorrhages diagnosed only at autopsy were excluded. A total of 125 hemorrhages were reported on the master forms as occurring during the period of observation. Of these, 24 began when the patients were not on anticoagulant therapy and another five occurred when heparin or Paritol were in effect and are excluded as not pertinent to the problem under study. One other, occurring when both Tromexan and dicumarol were in effect, had to be omitted since it could not be allocated to either anticoagulant. The remaining 95 of these occurred when Tromexan or dicumarol alone was in effect. These were studied intensively. Figure 6 presents the over-all picture with special emphasis on the relation of the episodes to anticoagulants. The group termed "episodes not related to anticoagulants" consists of 10 episodes under Tromexan and seven under dicumarol that were due to other causes that were sufficient to explain the full extent and severity of the hemorrhage. The rates per 1000 days of therapy were similar and serve only to confirm the approximate comparability of the groups in respect to susceptibility to bleeding. The remaining episodes were believed to be related to anticoagulant therapy. Those without other causes competent to produce hemorrhages and believed under the circumstances to be caused by anticoagulant therapy, were classified as "due to anticoagulants." Those arising from a known hemorrhagic site but in which the bleeding

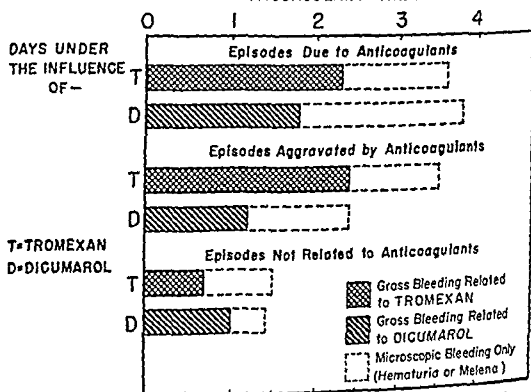


Figure 6. Number of bleeding episodes due to, aggravated by, or unrelated to, anticoagulant therapy beginning on days when patients were under the influence of Tromexan or dicumarol per 1000 days of corresponding type of anticoagulant therapy.

appeared aggravated by, precipitated by, or prolonged by, anticoagulant therapy were classified as "aggravated by anticoagulants." The resulting rates, based on 6,642 days of therapy with Tromexan only and 5,006 days of dicumarol only, showed the rate for gross hemorrhages due to anticoagulants to be 2.3 per 1000 days for Tromexan and 1.8 per 1000 days for dicumarol. Episodes aggravated by anticoagulants showed a rate of 2.4 gross bleeding episodes per 1000 days for Tromexan and of 1.2 similar episodes per 1000 for dicumarol The total for Tromexan for gross episodes related to anticoagulants is therefore 4.7 per 1000 days and that for dicumarol, 3 0 per 1000 days.[nn] The difference in each case is small, amounting to less than 2 episodes per 1000 days of anticoagulant therapy, or approximately 3 to 4 additional episodes per 100 patients treated for 20 days each. Evaluation of this small difference is difficult

As a first step in appraisal, statistical corrections for certain known differences between the two samples were undertaken for hemorrhage rates in the same manner previously described for thromboembolic complication rates.[oo] It was found that these corrections made only very minor changes in the rates quoted.[pp] The rate for gross hemorrhages related to Tromexan was raised from 4.7 to 4.8 per 1000 days while the gross rate for dicumarol remained unchanged. Other changes were similarly small. Clearly those obvious sampling differences for which corrections were feasible do not account for the differences noted.

A further test indicated that the difference also was not produced by the addition to the sample of the Tromexan cases collected without alternation with dicumarol since the amount of the difference remained about the same when these "special" (nonalternate) cases were excluded.[qq]

Whether the difference in corrected rates for gross hemorrhages related to the two anticoagulants of 1.8 per 1000 days was due to chance was also tested. The probabilities were found to favor explanation in terms other than chance,[rr] but explanation on a chance basis could not be ruled out with the degree of certainty that is conventionally implied by the term "statistically sig-

[nn] For comparison of rates with the dicumarol study, microscopic hemorrhages must also be included and original diagnoses other than myocardial infarction omitted When this is done, the Tromexan rate becomes 6 7 and the dicumarol rate becomes 6.3 per 1000 days of anticoagulant therapy. Both these rates are about double the comparable rate of 3.3 hemorrhages per 1000 days of anticoagulant therapy in the original dicumarol study The higher rate probably reflects primarily the higher prothrombin times maintained in the present study and secondarily, perhaps, better reporting of hemorrhages

[oo] See footnote bb, p. 470 for explanation of the method employed.

[pp] The process of correction left the microscopic hemorrhage rate for Tromexan unchanged (2.4 per 1000 days) and changed the dicumarol rate from 3.2 to 3.3 per 1000 days The total rate for Tromexan (gross plus microscopic) became 7.2 instead of 7 1 per 1000 and the total rate for dicumarol, 6.3 instead of 6 2 per 1000. All rates refer to hemorrhages due to, aggravated by, or precipitated by, anticoagulants per 1000 days of anticoagulant therapy of a given type.

[qq] Among the alternate series cases, the number of gross hemorrhages related to Tromexan per 1000 days of therapy with Tromexan only was found to be 5 1 and the corresponding rate for dicumarol to be 3.5 per 1000 The "special" (nonalternate) cases showed a rate of 3.9 for Tromexan. The 21 dicumarol cases in the nonalternate group showed no gross hemorrhage but the rate is meaningless in this case because of the small number in the group.

[rr] The chances were found to be about 9 per 100 that a difference equal to the difference (as corrected below) and in this direction would occur on a chance basis To apply the test it was necessary for statistical reasons to convert the corrected rates into a true proportion (the proportion of total days of therapy on which hemorrhages began) by deducting for two or more hemorrhages beginning on the same day. This [illegible]

[illegible] day in the same patient, whereas there was no more than one gross hemor-

nificant."[illegible] Nevertheless, since such a difference would become statistically significant if it persisted in a larger sample, it does not appear sound to pass it over without a full examination of the components which comprise these totals.

It should be noted first that the difference appears only with respect to gross hemorrhages. From figure 6, where microscopic bleeding is shown by dotted extensions of each bar, it is apparent that the difference does not extend to microscopic bleeding, for a larger proportion of the total hemorrhages under dicumarol than under Tromexan were microscopic in character.[illegible] Unfortunately, the rates for microscopic hemorrhages are greatly dependent on the frequency of laboratory examinations of urine and stools and there is no assurance that the two groups were examined in this manner with equal frequency. Therefore no great reliance should be placed on these dotted extensions, which in any case represent in most cases only minor and insignificant bleeding. Furthermore, a large experience with anticoagulants has demonstrated that microscopic hemorrhages are usually of little or no importance. For this reason, although microscopic bleeding is shown by dotted extensions in all charts, the textual discussion refers largely to gross bleeding.

Figure 7 presents graphically the severity of the bleeding episodes. Those termed "mild" include microscopic hematuria and occult melena and slight or transient but visible bleeding from any site. "Moderate" bleeding includes visible and more prolonged bleeding, but bleeding often untreated and without threat to life. "Severe" bleeding represents episodes that were excessive and dangerous and often required emergency treatment. When microscopic hemorrhages were included, 68 per cent of the bleeding episodes under Tromexan and 71 per cent of those under dicumarol were mild. The difference is of no consequence. Again, gross bleeding in both the mild and moderate categories was somewhat more in evidence under Tromexan than under dicumarol, but the difference was greater in the mild category of gross bleeding. Three severe hemorrhages related to anticoagulants were diagnosed under each drug. The three under Tromexan were all considered due to the drug.[illegible] In the case of the three for dicumarol, other underlying pathology was present in two. Fatal hemorrhages and hemorrhages diagnosed at autopsy only are discussed elsewhere.

The types of bleeding that compose these totals are shown in figure 8. It will be noted that hematuria is the commonest manifestation of bleeding from both drugs and that more than half of the hematuria episodes were microscopic only. Both the gross and microscopic rates for hematuria are remarkably close for both drugs. The contrast in hemoptysis is less significant than would appear, for three of the five cases that constitute the Tromexan column for this type of bleeding occurred in the presence of

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rhage on the same day in the case of dicumarol. The test necessarily assumes also that the record for each day is independent of that for every other day, which is not, strictly speaking, true since more than one day was observed for each patient; corrections for this characteristic of the data were not feasible, but if undertaken would have reduced slightly the probabilities of significance quoted.

[illegible] The conventional definition requires that there be less than 1 or 2 chances (or at least less than 5) in 100 that the difference could occur on a chance basis before the difference is termed "statistically significant"; however, the confidence level adopted is the responsibility of the authors and the choice should rest ultimately on the direction in which an erroneous interpretation would have the more serious consequences.

[illegible] When laboratory reports showed 15 or more red blood cells per high power field, microscopic hematuria was recorded, the period from the beginning of observation of hematuria until the urine had cleared being counted as one episode, [illegible] number of labora- [illegible] was similar with [illegible] aiac or over being [illegible]

[illegible] Counts exclude one case treated with Tromexan showing severe hemorrhage in several sites at autopsy (see *Deaths Occurring during Study*), since this bleeding was not diagnosed clinically.

pulmonary infarction. All were mild except one which required treatment with vitamin K and whole blood. Tromexan showed slightly more severe gastrointestinal bleeding than dicumarol, although there was a greater reported incidence of occult (guaiac test) bleeding with dicumarol. The difference in epistaxis is a matter of five episodes versus one, mostly mild. For bleeding of other types the rates are identical. This miscellaneous group includes uterine bleeding related to anticoagulants, bleeding from sites of operations or from hematoma, bleeding gums, and one each of the following: cerebral hemorrhage, ecchymoses, and petechial hemorrhage.

Gross hemorrhages due to anticoagulants were also compared as to duration,** measured roughly in terms of the number of different days on which bleeding was in evidence. The averages were practically identical for the two drugs, two and four-tenths days for dicumarol and two and three-tenths days for Tromexan. In general, when hemorrhage appeared and the drug was stopped promptly, bleeding tended to subside within 24 to 48 hours under both drugs when there was no underlying pathology conducive to bleeding. Although the prothrombin time fell more rapidly after cessation of Tromexan than of dicumarol,

** Since the recorded duration of a microscopic hemorrhage is greatly influenced by the frequency of laboratory examinations, data on duration are not presented for such hemorrhages. Similarly, duration data for hemorrhages aggravated by anticoagulants are not discussed because it was too difficult to evaluate how many of the total days of such a hemorrhage were due solely to the underlying condition and how many were aggravated by anticoagulants

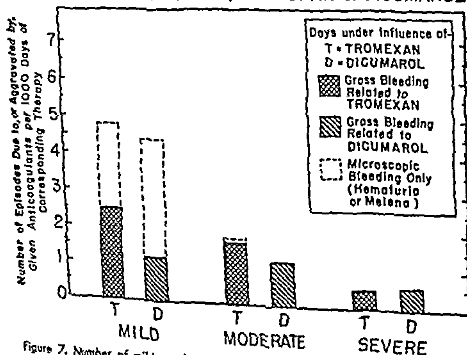


Figure 7. Number of mild, moderate, and severe bleeding episodes due to, or aggravated by, anticoagulant therapy beginning on days when patients were under the influence of Tromexan or dicumarol per 1000 days of corresponding anticoagulant therapy.

the hemorrhages did not always wane proportionately, sometimes persisting for a few days after the prothrombin times had regained low levels. Such continued bleeding was usually minor and not a threat to the patient. Synthetic vitamin K preparations were employed in 34 per cent of the episodes of hemorrhage related to Tromexan and 16 per cent of the episodes related to dicumarol. It appeared beneficial, but, because of differences in dosage, nature of bleeding, and so forth, no comparison of its use between the two drugs seemed justifiable.

It is well known that anticoagulant bleeding parallels the rise of prothrombin time. A substantial increase in incidence was found in the dicumarol study to begin at about 50 seconds (7 per cent) and a larger increase to occur above 60 seconds (6 per cent or less).[15] The question arose, therefore, whether the slightly higher rate noted for Trome
occurred at all prothrombin levels or onl
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readings shown in figure 9 are low becau
about 97 per cent of the prothrombin tim
also fell in this range. Although bleeding d
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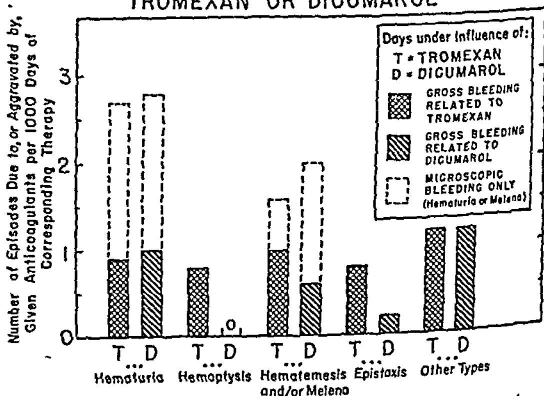


Figure 8. Number of bleeding episodes of specific types beginning on days when patients were under the influence of Tromexan or dicumarol only and considered due to, or aggravated by, these anticoagulants per 1000 days of anticoagulant therapy.

urred at all levels, bleeding in the presence f underlying pathology showed a tendency o begin at lower levels than bleeding due olely to anticoagulant therapy. Persistent leeding in this range should instigate an nvestigation of the possibilities of causes other than anticoagulants (for example, malignancy[26]).

At times above 50 seconds the incidence of bleeding shot up dramatically, as figure 9 indicates. Under Tromexan there were 197 days with recorded times at these levels during which nine gross and three microscopic hemorrhages related to Tromexan began, a rate of 46 gross hemorrhages and 61 total hemorrhages per 1000 days. On the 75 dicumarol days known to have reached 50 seconds or more, two gross and two microscopic hemorrhages related to dicumarol also began, a corresponding rate of 27 gross hemorrhages and 53 total hemorrhages per 1000 days. Because the number of days at these high levels was limited, the difference may be a chance one. On the other hand, this difference may arise from the fact that a somewhat larger proportion of the Tromexan prothrombin times above 50 seconds were excessively high and bleeding would be expected to occur in such zones. These occasional high times, plus the higher proportion of all Tromexan readings in the zone of 50 seconds and above, appear to be the two most reasonable explanations, other than chance, for the higher overall bleeding rate for Tromexan.

A further bit of evidence pointing toward the difficulties in control as the underlying cause of the differential noted is the fact that the differences between the two drugs in rates of gross bleeding was greatest during

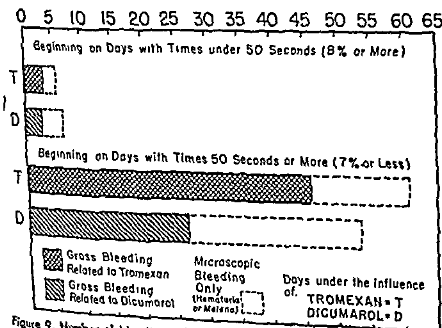


Figure 9. Number of bleeding episodes due to, or aggravated by, anticoagulant therapy beginning on days when patients were under the influence of Tromexan or dicumarol and showed times under 50 seconds and 50 seconds or more per 1000 days of anticoagulant therapy characterized by times at similar levels.

the hemorrhages did not always wane proportionately, sometimes persisting for a few days after the prothrombin times had regained low levels. Such continued bleeding was usually minor and not a threat to the patient. Synthetic vitamin K preparations were employed in 34 per cent of the episodes of hemorrhage related to Tromexan and 16 per cent of the episodes related to dicumarol. It appeared beneficial, but, because of differences in dosage, nature of bleeding, and so forth, no comparison of its use between the two drugs seemed justifiable.

It is well known that anticoagulant bleeding parallels the rise of prothrombin time. A substantial increase in incidence was found in the dicumarol study to begin at about 50 seconds (7 per cent) and a larger increase to occur above 60 seconds (6 per cent or less).[15] The question arose, therefore, whether the slightly higher rate noted for Tromexan occurred at all prothrombin levels or only at high levels. Figure 9 demonstrates the findings in this regard. The gross hemorrhage rates for Tromexan and dicumarol were nearly identical for prothrombin times below 50 seconds, namely 3.5 episodes related to anticoagulants per 1000 days with known prothrombin times for Tromexan versus a corresponding figure of 3.1 per 1000 for dicumarol. Basically, the incidence of hemorrhage at these levels would appear to be the same for the two drugs. Actually, these are the levels at which most of the bleeding began (that is, 79 per cent of the episodes) but the incidence per 1000 days with such readings shown in figure 9 are low because about 97 per cent of the prothrombin times also fell in this range. Although bleeding due solely to anticoagulants occasionally oc-

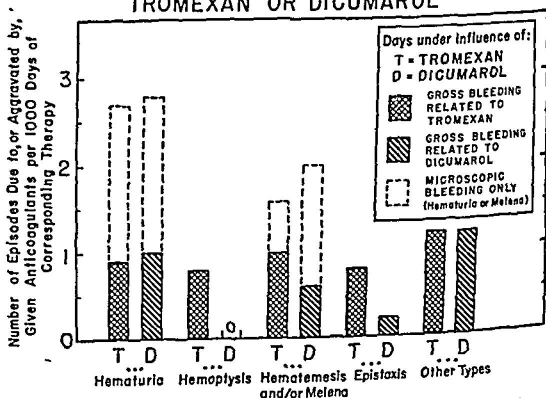


Figure 8. Number of bleeding episodes of specific types beginning on days when patients were under the influence of Tromexan or dicumarol only and considered due to, or aggravated by, these anticoagulants per 1000 days of anticoagulant therapy.

tein nitrogen), (4) blood cholesterol. Although these tests were not performed at sufficient intervals to be satisfactory for a precise statistical evaluation of minor changes, no gross evidence of toxicity resulting from the use of Tromexan or dicumarol was found, either in our own review of the individual laboratory results or from the statements of the physicians participating in the study. Rarely a slight rise in nonprotein nitrogen (or urea) has been noted during the use of both drugs, but these have occurred in the presence of renal pathology. The significance of a relationship to anticoagulants has in each instance been doubtful. One patient in serious shock from myocardial infarction developed renal shutdown which coincided with the initial dose of Tromexan. The shock appeared to be an adequate cause for this complication. The administration of either drug in the face of shock and oliguria may result in very rapid and dangerous elevations of the prothrombin time.[24] Figure 10 illustrates this rapid prothrombin response in the setting of renal shutdown and its treatment with vitamin K_1 oxide.[25] Heparin has also produced excessive response when administered in the presence of shock. Even in the presence of severe renal disease no significant alteration in the chemical findings were noted in this series from the administration of Tromexan or dicumarol.

The Effects of Other Drugs on Anticoagulants

The doses of xanthines, salicylates, penicillin, and adrenocorticotropic hormone used

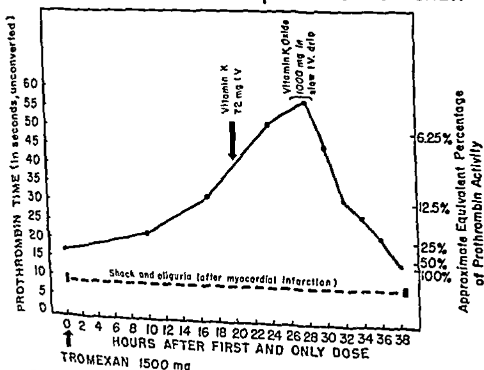


Figure 10. Excessive response to Tromexan in patient with myocardial infarction and subsequent shock with oliguria. (Excessive hypoprothrombinemia occurred 28 hours after a single 1500 mg. dose of Tromexan. Note lack of effect of water-soluble vitamin K and subsequent rapid response to vitamin K_1 oxide.)

the first two weeks of the illness (5.9 vs. 3.5), decreased in the third and fourth week (4.0 vs. 3.3), and by the fifth week and later was eliminated (2.6 vs. 2.5).[ww] Although explanation on a chance basis cannot be conclusively ruled out, it seems more reasonable to attribute this decreasing difference to the higher prothrombin times which often occurred early in Tromexan administration before experience with a given patient's particular reaction pattern had been gained. As the times were stabilized, the risk of hemorrhage diminished. With the use of divided daily doses, particularly during the initial weeks, it should be possible to improve substantially on the hemorrhage record herein presented for Tromexan.

Toxic Reactions

The causal relationship of symptoms to specific drugs, especially when several drugs are being administered simultaneously to ill patients, is extremely difficult to evaluate. The reactions noted below include only those in which there appeared a logical relationship to the anticoagulants.

Tromexan is dispensed in 150 and 300 mg. tablets. The pill, like dicumarol, is slightly bitter to the taste, although not objectionably so. Occasionally it is responsible for mild systemic reactions. The following reactions to Tromexan have been noted by the observers in this study:

Nausea	7	Urticaria	2
Vomiting	2	Maculopapular rash	2
Diarrhea	2	Dyspnea	1

A total of 12 patients, or 4.2 per cent of all patients receiving Tromexan, showed one or more such reactions.

The only reaction clearly related to dicumarol in this series was one episode of nausea and vomiting. (This case constitutes 0.4 per cent of all patients receiving dicumarol.) It is possible that more reactions occurred with dicumarol but were not reported, as less attention would be paid to minor gastrointestinal symptoms occurring with this drug than in the case of Tromexan which was undergoing its first clinical trial in many of these institutions.[xx]

An interesting though incidental observation reported from the Henry Ford Hospital[yy] was the apparent relief of cardiac angina by Tromexan. The patient, a 62 year old male, was admitted to the hospital with decubitus angina and "acute coronary insufficiency." It was noted that dicumarol, given prophylactically, exerted no beneficial effect on the angina during his hospital course. Shortly after discharge the patient suffered a myocardial infarction and on rehospitalization was given Tromexan in lieu of dicumarol. For the next three weeks, while the patient was on Tromexan, the pain disappeared. On reinstitution of dicumarol for one week, the pain reappeared, and a switch back to Tromexan resulted in a disappearance of the angina which has not recurred since ambulatory Tromexan therapy. The significance of this is not clear, in view of the psychic factors and vagaries of cardiac angina. Reports of the beneficial effects of dicumarol and heparin on angina have appeared.[22, 23] No previous report exists of similar effects from Tromexan.

Laboratory Evidence of Toxicity

Since previous work had revealed aggravation of hepatorenal dysfunction following Tromexan administration,[14] a number of laboratory tests were included in the study. In addition to the routine blood count, urine and stool studies, the following were studied: (1) sedimentation rate, (2) liver function [illegible] tion tests (phenolsulfonphthalein, [illegible]

[ww] These figures omit both days and hemorrhages in cases for which the date of onset was unknown.

[xx] The episode of dyspnea was associated with nausea, vomiting and urticaria following an initial 1500 mg. dose of Tromexan.

[yy] Carefully reviewed by Dr Lawrence Denham, Resident Cardiologist at that Hospital.

tein nitrogen), (4) blood cholesterol. Although these tests were not performed at sufficient intervals to be satisfactory for a precise statistical evaluation of minor changes, no gross evidence of toxicity resulting from the use of Tromexan or dicumarol was found, either in our own review of the individual laboratory results or from the statements of the physicians participating in the study. [illegible]

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The Effects of Other Drugs on Anticoagulants

The doses of xanthines, salicylates, penicillin, and adrenocorticotropic hormone used

Effect of Shock on the Response to Tromexan

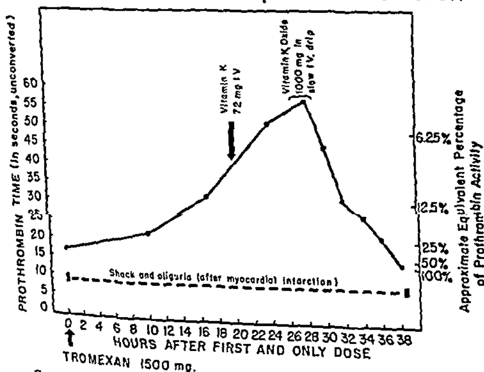


Figure 10. Excessive response to Tromexan in patient with myocardial infarction and subsequent shock with oliguria. (Excessive hypoprothrombinemia occurred 28 hours after a single 1500 mg. dose of Tromexan. Note lack of effect of water-soluble vitamin K and subsequent rapid response to vitamin K_1 oxide.)

in this study exerted no obvious influence on the prothrombin time following Tromexan or dicumarol. The use of *aureomycin* and *terramycin apparently had a profound effect on the prothrombin response to these drugs, noted in four cases in our series.* In one case when aureomycin and terramycin were administered shortly before the anticoagulant, the prothrombin time rose excessively after the usual *initial* dose of anticoagulant and had an unusually delayed fall (fig. 11). In three cases when the antibiotic was given during the course of anticoagulant therapy, a diminution in the dosage of the drug was necessitated to keep the prothrombin time within the therapeutic range. Although no study of this relationship has been carried out, it has been suggested that sterilization of the gastrointestinal tract by the a biotics interferes with the production of v min K by intestinal bacteria.[20] Failur moderate the dosage of coumarin derivat when these antibiotics are being used r result in dangerous prothrombin times consequent hemorrhages.

Deaths Occurring during the Stud

There were 44 deaths reported in this se of which 42 occurred within six weeks of date of onset (or hospitalization).** (E other deaths reported from the various h pitals were not included as they occur

** Date of hospitalization was used when date of onset had not been reported and could be estimated.

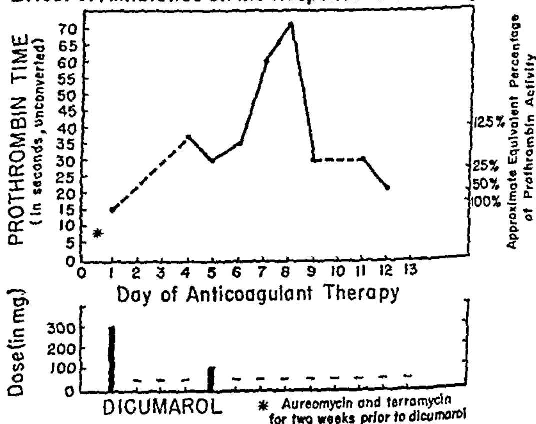


Figure 11. Case illustrating marked hypoprothrombinemia after small doses of dicumarol. (Patient had taken aureomycin and terramycin for "gastroenteritis." He developed thrombophlebitis of the leg shortly after this had subsided. Note the slow return of the hypoprothrombinemia toward normal. Dotted extensions denote lack of available prothrombin times.)

after the period of study.) Table 2 previously presented shows the breakdown of deaths within the period of observation by the different diagnostic groups. Because of the variety of thromboembolic illnesses, the small numbers in some diagnostic groups, and the varying periods of observation, the data furnish an unsound basis for death rates in a statistical sense, with the possible exception of myocardial infarction.

Deaths among Myocardial Infarction Cases

The counts are too small in most categories to use to compute the percentage dying by diagnostic groups and are unsuitable in other respects for case rates and for comparisons between Tromexan and dicumarol. To enable the reader to identify the type of sample involved, it is reported that omitting deaths after six weeks and in mixed drug cases, 10.8 per cent of the 139 myocardial infarction cases treated with Tromexan are known to have died within six weeks of the time of onset of the attack and 14.2 per cent of the 106 myocardial infarction cases treated with dicumarol.[aaa] The difference in deaths under the two anticoagulants may reflect the higher proportion of cases mild at onset in the Tromexan group and other miscellaneous differences in sampling, as well as the operation of chance factors. Also the dicumarol rate is increased slightly by the deaths that occurred coincidentally with Paritol supplementation of dicumarol reported in the subsequent discussion.[bbb] Neither of these above percentages may be used justifiably to evaluate the relative merits of the two drugs since the deaths in most cases were related only indirectly, or not at all, to the type of anticoagulant employed. Both percentages are below the experience in the study of dicumarol in myocardial infarction[11] in which deaths within six weeks amounted to 16.0 per cent of the total treated group;[ccc] close comparison is not warranted because of the difference in the cases sampled and the differences in length of observation and timing and length of anticoagulant therapy.

Of the 31 deaths in patients with myocardial infarction, 14 died in heart failure, three died of embolic phenomena, three died of extension of the previous infarct or fresh infarction, two died in uremia, one of a ruptured interventricular septum, and one of a ruptured myocardium and hemopericardium (autopsy). In seven patients the cause of death was not ascertained. These latter patients died suddenly during the hospital course and no autopsies were performed. Four of the 31 deaths were related to anticoagulants and will be described in detail. One case of myocardial rupture was reported, and one case of rupture of the interventricular septum. (Both patients were on dicumarol and both episodes occurred on the fourth day of therapy as the prothrombin time was entering the therapeutic range.)

Among the coronary group, death due to thromboembolism occurring during anticoagulant therapy was established in only three patients.[ddd] These were all due to peripheral emboli, as the deaths caused by extension of a previous infarction or a new infarct (a total of three) occurred in each case after anticoagulants were stopped. One patient on dicumarol and in the therapeutic range for the previous three days, died shortly after an embolus to the leg. Prior to that the prothrombin time was in the thera-

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[aaa] These percentages may understate slightly actual deaths since not all myocardial infarction cases were followed six weeks, but the error should be small since deaths shortly after hospital discharge are usually reported to the hospital or physician concerned.

[bbb] When the two deaths in which Paritol may [illegible]

[ccc] This rate includes cases denied dicumarol because of medical contraindications. When these are omitted, the rate becomes 15.2 per cent.

[ddd] It is possible that some further deaths due to thromboembolism are included among cases dying of unknown causes.

peutic range approximately 50 per cent of the time, the remainder being below the therapeutic range. Two other patients died of cerebral emboli following myocardial infarction while on Tromexan. One patient suffered a cerebral embolus the day after a massive infarction and 18 hours after the first dose of Tromexan. The prothrombin time had reached 35 seconds, due to shock and resulting oliguria in this patient. In the other case a cerebral embolus occurred on the eighteenth day following infarction. The prothrombin time was 30.0 seconds on the day of the embolus, but previously the prothrombin time was less than the therapeutic range 80 per cent of the course.

It is of interest that the three myocardial infarction cases who died of extensions or new myocardial infarctions (as shown by definite electrocardiogram changes or by autopsy) developed these after the cessation of anticoagulants. Two patients who had received Tromexan for the initial infarction, one for two weeks and the other for five weeks, developed a recurrence on the third day following the cessation of Tromexan. In the one patient who died of a fresh infarction following dicumarol, the incident occurred on the tenth day after dicumarol was stopped (patient received dicumarol for four weeks).

Deaths in the Noncoronary Group

Of the 13 deaths which occurred in cases other than myocardial infarction, only two were believed to be due to thromboembolic accidents occurring during the period of anticoagulation.[***] Both of these cases were treated with Tromexan. Both illustrate the occasional failure of anticoagulants to eliminate such risks. One patient in cardiac failure secondary to old rheumatic heart disease with subsequent phlebothrombosis of the right leg developed phlebothrombosis of the left leg while at an adequate prothrombin time and shortly thereafter died of a "probable" pulmonary infarction. The prothrombin times were satisfactory except for two readings slightly below the therapeutic range on the third and fourth day before death.[†††] No autopsy was performed. In the second instance[‡‡‡] a patient with arteriosclerotic heart disease and a recent pulmonary infarction suffered a second pulmonary embolism eight days after the first with prothrombin activity at about 6 per cent for the previous three days. No reading was obtained on the day of death as the patient died early in the morning. At autopsy a fresh pulmonary embolism was found. Death had occurred so rapidly from this that no infarction had as yet formed.

Autopsy Material

Complete autopsy protocols were received in 14 of the 44 fatalities. Ten of these were cases of myocardial infarction, three of pulmonary embolism, and one of multiple cerebral emboli of unknown origin. In the myocardial infarction group six cases received Tromexan and five received dicumarol (two Tromexan cases and one dicumarol case also received heparin initially). While the smallness of the group prohibits any statistical appraisal, certain facets of the autopsy reports are of interest. The protocols were examined for evidences of mural thrombi subsequent to the infarction, and in those cases where such thrombi were present, for the relation of these to the anticoagulant control. Of these 10 myocardial infarction cases, nine cases failed to demonstrate any intracardiac thrombi. In these [illegible] control was con- [illegible] that the [illegible] prothrombin time was in the therapeutic zone approximately 75 per cent of the total

[***] As before, only cases where the diagnosis of thromboembolic complications appeared rather definite are considered.

[†††] The prothrombin time was not completely adequate for the three-day period.

[‡‡‡] Not included in section on complications because embolism was diagnosed at autopsy, not clinically

anticoagulant period, and particularly during the first week when the incidence of embolic phenomena is at the highest.[hhh] That these patients were adequately maintained on anticoagulants was further evidenced by the following: out of a total of 119 prothrombin determinations in these nine cases, only 33 were considered below the therapeutic range (27 per cent of the total) and very few of these occurred on successive days, where the possibility of thrombotic phenomena is greater than when these low times were sporadic as was the case here.

In the one myocardial infarction case that demonstrated a superimposed mural thrombus the patient had been on Tromexan. Because of the uncertain date of the infarction, it was not possible to determine whether this developed in the face of adequate anticoagulant therapy.

Among the four autopsies performed in the nonmyocardial infarction cases, there was one instance of a demonstrable clot formation under anticoagulant therapy. This was described above as the pulmonary embolus occurring under apparently adequate Tromexan therapy.

Because of the small amount of autopsy material, no definite conclusions concerning the relative prophylactic powers of the two drugs can be drawn. In the myocardial infarction group the extremely low incidence of mural thrombi conforms with the former observations that adequate anticoagulants diminish the incidence of this complication. The isolated pulmonary infarction episode must be considered a pure anticoagulant failure.

Possible Anticoagulant Deaths

Deaths related to anticoagulant hemorrhage are a major concern during such therapy. This toxic effect of anticoagulants appeared intimately connected with the death of four patients in this series. In two of these the combined use of Paritol (a heparin-like synthetic polysaccharide) and dicumarol were thought to have participated in the deaths by causing cerebral hemorrhages. Both patients had elevated clotting time (due to Paritol) in the face of massive myocardial infarction with hypotension and oliguria. In the first patient the prothrombin time was 54 seconds (not converted)[iii] before death and an ecchymotic rash appeared over the face and thighs prior to death. It was the clinical impression of the attending physician that Paritol[jjj] and possibly dicumarol contributed to death in this case. The other patient on dicumarol plus Paritol expired 24 hours after admission with a clotting time of 160 minutes and a prothrombin time of 22 seconds. The possibility of cerebral hemorrhage was also considered in this case. Autopsies were not performed in either case. Because of the concomitant use of Paritol, the role of dicumarol cannot be assayed in these cases.

Tromexan appeared to be a cause of death through hemorrhage in two patients. They are herewith described in detail. A 44 year old male was admitted to the hospital for observation of vague upper abdominal pain. He had rheumatic heart disease and was fibrillating. On his thirteenth hospital day a cerebral accident occurred. This [illegible] to be [illegible] admir[illegible] first day, then successively 1200, 600 and 900 mg. over the following three days (fig. 12). On the fifth day after starting Tromexan the prothrombin time was 140 seconds (2 per cent) and the drug was stopped. On the following day gross hematuria appeared. The prothrombin time fell slowly and four days later was still 69 seconds (7 per cent). On this day nuchal rigidity appeared and a diagnosis of subarachnoid hemorrhage was

[hhh] In the original dicumarol study[18] mural thrombi were found in 32 per cent of the cases treated with dicumarol and examined at autopsy and in 63 per cent of the control cases that had received no anticoagulant therapy

[iii] The clotting times were not available.

[jjj] The Paritol used in this study was an early experimental lot.

made. Large doses of vitamin K were given and the prothrombin time fell to 25 seconds the following day. However, the patient expired in a few days. A post-mortem examination revealed the following: mitral stenosis without auricular thrombi, numerous old and recent renal infarcts, focal hemorrhages in the lungs, a diffuse subarachnoid hemorrhage with no evidence of local arterial or venous pathology. No embolus was demonstrated.***

A 65 year old female with arteriosclerotic and hypertensive heart disease was admitted to the hospital in acute pulmonary edema. She was put on Tromexan because of a suspected myocardial infarction. (Left bundle branch block was present.) Her progress was considered fair, but on the tenth hospital day she expired suddenly. She had been in the therapeutic range throughout her course on a daily dose of 900 or 1200 mg. of Tromexan. Her prothrombin level was 12 per cent on the day of death. An autopsy revealed an old healed myocardial infarction (over four months) and a healing infarction of one to two months duration. Striking features were the large areas of hemorrhage throughout the healed infarct, also hemorrhages in the right upper and right lower lobes of the lung, and in the spleen. The cranial cavity was not explored. There was no known bleeding tendency. The immediate cause of death was considered to be probably heart block but multiple hemor-

*** It is therefore at least possible that the original cerebral accident was a hemorrhage prior to the use of any anticoagulant and that the Tromexan aggravated this. This case illustrates (a) the need for very careful diagnosis of cerebral lesions before the administration of anticoagulants and (b) the need for more careful control of the administration of anticoagulants.

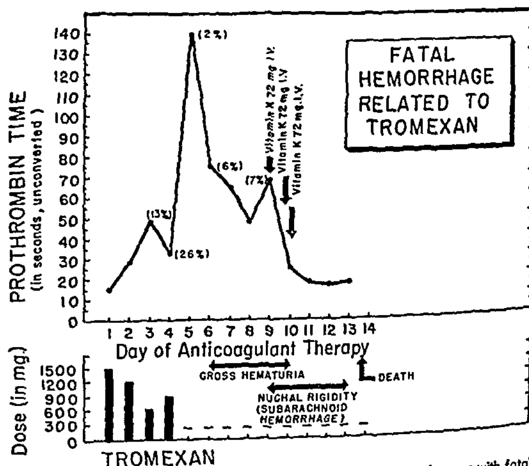


Figure 12. Case of subarachnoid hemorrhage during Tromexan therapy with fatal outcome.

rhages and the possibility of intracranial hemorrhage were not ruled out.

Among the other thromboembolic groups, one other patient died of a subarachnoid hemorrhage. This patient, a 58 year old male, a cerebral spastic with quadriplegia, was given Tromexan because of a thrombophlebitis of the left leg. After two weeks of Tromexan, during which time his prothrombin time did not exceed the therapeutic range, the drug was discontinued. Five days later, when the prothrombin time had fallen [illegible] .neous [illegible] was a lethal factor in two of the above cases appears likely. In the dicumarol cases, the simultaneous use of Paritol renders it difficult to evaluate the role of dicumarol. In the first Tromexan case hemorrhage seems related to the marked prolongation of the prothrombin time.[III] In the second patient the cause of the extensive bleeding without unusual prolongation of the prothrombin time is not clear and an undiagnosed hemorrhagic diathesis may have been present, potentiating the effects of Tromexan. In the third patient the occurrence of hemorrhage with a prothrombin time that was practically normal *suggests* the relationship to Tromexan is fortuitous. Such instances serve as a dramatic *re-emphasis* that anticoagulant therapy *warrants constant* meticulous attention. Dicumarol has recently been reported as a leading cause of death due to drugs.[31] Many of these fatalities were due to faulty use of this drug and therefore should be preventable in the future.

[III] This case is instructive in illustrating the pitfalls of anticoagulant therapy (fig. 12). Administration of a larger dose of Tromexan in the presence of an elevated prothrombin time (fourth day) resulted in a more serious prolongation of the time. The hematuria occurring at such elevated times merited *more* rigorous antidotal therapy (vitamin K_1, blood, etc) as these persistent high elevations in the prothrombin time are a real hazard to a patient.

Summary and Conclusions

This study was designed to evaluate the relative merits of Tromexan and dicumarol for anticoagulant therapy. A total of 514 patients with actual or threatened thromboembolic conditions were treated with one or both of these anticoagulants. A total experience of 6,642 days of Tromexan therapy and 5,006 days of dicumarol therapy without supplementation with other anticoagulants was reviewed and analyzed. Responsible investigators from seven hospitals cooperated in the project by reporting each individual case on a detailed master form to the Central Laboratory. Analysis of findings from these cases has resulted in the following conclusions as to the relative advantages of the two anticoagulants:

1. Previous reports that a more rapid initial prolongation of prothrombin times can usually be achieved with Tromexan than with dicumarol have been confirmed. This characteristic makes it possible to protect the patient more rapidly with Tromexan than with dicumarol in the initial stages of anticoagulant therapy when the risk of thromboembolic complications is usually especially high, as well as after a lapse in therapy when a rapid return to therapeutic levels is indicated.

2. Previous reports that prothrombin times usually return more rapidly to normal after the cessation of Tromexan than after cessation of dicumarol have been confirmed in a variety of circumstances. This characteristic of Tromexan is of advantage when it becomes advisable to terminate therapy, as when excessively prolonged times, with or without bleeding, develop or when emergency surgery becomes necessary.

3. The power of the two anticoagulants to protect the patient from thromboembolic complications appeared about equal, as demonstrated by the close similarity in the thromboembolic complication rates for days of therapy under each of the two anticoagulants.

4. More of the thromboembolic complications under Tromexan occurred when prothrombin times were below the optimal therapeutic range than did those under dicumarol. This suggests that control of the lower limits of the therapeutic range presents more of a problem with Tromexan than with dicumarol.

5. Mild toxic reactions (nausea, diarrhea or rashes) were infrequent, being reported in 12 (4.2 per cent) of the patients treated with Tromexan and in one (0.4 per cent) of the patients treated with dicumarol. These reactions did not constitute a significant disadvantage in the use of either drug.

6. A review of the laboratory test findings for all patients failed to reveal any evidence that either Tromexan or dicumarol produced significant evidence of toxicity in the doses commonly used for therapy.

7. Fourteen autopsies were studied in detail. These did not reveal any difference in the toxicity of the two anticoagulants or in their effectiveness in preventing thromboembolic complications.

8. A higher proportion of total prothrombin times were 50 seconds or more (7 per cent or less) during Tromexan therapy than during dicumarol therapy. These were mostly encountered in patients on a single daily dose.

9. This tendency to excessive response was reduced markedly in those patients who received Tromexan in divided daily doses.

10. The total rate of gross hemorrhage related to anticoagulants was slightly higher during Tromexan therapy than during dicumarol therapy. This difference was found primarily at times of 50 seconds or over and during the early stages of anticoagulant therapy.

11. When observations were limited to days when prothrombin times were under 50 seconds (above 7 per cent), the incidence of hemorrhagic episodes due to, or aggravated by, the two anticoagulants appeared approximately similar, indicating that the observed differences in total hemorrhage rates (see item 10) were related to the more frequent upward fluctuations under Tromexan under single daily doses and not to some other inherent characteristic of this anticoagulant.

12. These combined observations (items 8 to 12) suggest that, when given in single daily doses, Tromexan is slightly more difficult to control than dicumarol. Experience with the daily total divided into two or three doses indicates that the prothrombin time is more satisfactorily controlled with this regimen than with single doses.

13. In this series of patients two deaths occurred in which Tromexan was probably implicated. In one of these, poor control of prothrombin times played a role. Two deaths occurred in patients who were on the combination of Paritol and dicumarol therapy. The clotting times were prolonged in both and the prothrombin times were 54 and 22 seconds respectively. It is difficult to assay the part played in these deaths by each of the two anticoagulants involved.

14. As with all coumarin derivatives and phenylindanedione, the prothrombin times of patients receiving Tromexan should be watched with especial care until the response pattern is fully evident. Thereafter the use [illegible] less super- [illegible]

15. The foregoing conclusions relate to the total experience with Tromexan and dicumarol when employed in a variety of thromboembolic conditions in the present study. In addition, some comparisons are possible with the findings of the previous study of the use of dicumarol in myocardial infarction.[18] Such comparisons require, however, the omission from the present study of patients with diagnoses other than myocardial infarction. These omissions reduce the sample to 262 patients, of whom 139 received Tromexan only; 106, dicumarol only; and 17, both anticoagulants. The following conclusions pertain only to this component of the total sample:

(a) Of the myocardial infarction patients

eceiving dicumarol only, 14.2 per cent died within six weeks of the date of onset as compared with 10.8 per cent of the patients receiving Tromexan only. Since two of the dicumarol deaths occurred in association with the combined use of Paritol and dicumarol, and since slightly more of the Tromexan cases were mild at onset, and for other reasons, these differences cannot be attributed to differences between the two anticoagulants. Both death rates are slightly below the 16.0 per cent record of deaths within six weeks in the treated group in the previous dicumarol study and very substan- ly below the 23.4 per cent of deaths oc- ring in the control group in that study.

(b) The thromboembolic complication tes for the myocardial infarction patients ere similarly favorable when compared ith the results of the previous dicumarol tudy. During Tromexan therapy in the resent study, thromboembolic complica- ions averaged 2.3 per 1000 days of therapy and during dicumarol therapy, 2.2 per 1000 days These day rates are both about one third lower than the corresponding rate of 3.1 complications per 1000 days during the period of dicumarol therapy in the previous study and significantly below the 12.6 rate per 1000 days for the control group in that study during days of their illness corresponding to the period of therapy for the treated group

(c) Thus the power of protection of the two anticoagulants in myocardial infarction does not vary greatly. When judged by comparison with the control group of the previ- us study, both produced significant reduc- ions in death rates and in the incidence of thromboembolic complications. The experience of this study with an additional 262 patients with myocardial infarction therefore constitutes further confirmation of the major conclusions of the original study.

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Method Used in Estimating the Number of ıromboembolic Complications and Deaths that Would Have Occurred in the Control Group if No Control Patient Had Received Any Anticoagulant Therapy

S indicated in Chapter III, 35 patients in control group were placed on anticoagu- t therapy following the development of a t, second, third, or fourth thromboem- lic complication. [illegible]

anned for the experiment and thus created statistical problem in the evaluation of the sults of anticoagulant therapy. To resolve e dilemma by transferring control cases ceiving anticoagulants after complications the treated group would have destroyed e comparability of the control and treated oups by weighting the treated group with excessive proportion of cases with a high cidence of complications. On the other nd, to have retained cases treated with ticoagulants in the control group without y adjustment for this treatment would ave meant that findings for the control roup could not have represented correctly e expected incidence of thromboembolic omplications and deaths without anti- oagulant therapy. The contrasts with the reated group would have been either less, r greater than, the true contrasts according o the actual effects of anticoagulants, the entral issue which the experiment itself was esigned to clarify. The least objectionable method available to meet the difficulty, therefore, appeared to be the development of statistical estimates of the number of deaths and complications that would have occurred among these 35 patients if they had never received anticoagulants and the use of these figures to correct the total control group rates. After a variety of experiments with alternative procedures, the following methods were adopted as the fairest and most reasonable for the realistic portrayal of the deaths and complications to be expected when no anticoagulants are used in a group comparable in basic composition to the control group in the present study.

ESTIMATES FOR COMPLICATIONS

The number of complications that the control group cases receiving anticoagulants would have developed without anticoagulants was estimated in two stages. In the first stage, it was assumed that cases receiving anticoagulants, if they had not received this therapy, would have developed complications at the same rate as did comparable cases in the control group who did not receive anticoagulants. Since all control patients receiving anticoagulants for whom an estimate was needed* had actually developed at least

* Some patients originally in the control group received anticoagulants on a preventive basis before the development of complications, but these

one complication outside the heart, *the most nearly* comparable group appeared to consist of all control group cases not receiving anticoagulants who developed at *least one* complication outside the heart. *Such cases* were therefore segregated *and the proportion in each age* subgroup *with* one complication who developed a second was computed; similarly, the proportion of those with two who developed three, *and the proportion* of those with three who developed four was computed. These rates were then applied to the appropriate age subgroups among those receiving anticoagulants to estimate the number of complications that would have developed without anticoagulants. For cases receiving anticoagulants after their first complication, estimates were prepared for the expected number of second, third, and fourth complications. For those receiving anticoagulants after their second complication, *estimates* were prepared of the expected number of third and fourth complications, the reported numbers being accepted for the first and second complications. For those receiving anticoagulants after their third complication, estimates were prepared only for the fourth complication.

The estimates resulting from stage one were necessarily too low on the average because they were based on the application of rates from a group with a known lower incidence of complications to a group with a known higher incidence. This was obvious since, even with anticoagulants, the control group cases receiving anticoagulants developed more actual complications on the average and a higher proportion developed multiple complications even before these corrections than was the case with the group used as a base for the estimates of rates.

Stage two of the estimating procedure was designed to correct, insofar as possible, for this understatement. This second stage was based on the *assumption that if no anticoagulants had been received*, the control *cases receiving* such therapy would, without *this* aid, have developed further thromboembolic complications during the period of therapy in the same proportion as did all cases in the control group developing at least one complication *outside the heart, including* (*in contrast to stage one*) those cases who had received anticoagulants. Since the actual number of complications in that component of this total group who received anticoagulants was influenced during certain periods by such therapy, stage two utilized in the computations the estimated numbers of complications without therapy derived from stage one as substitutes for the actual numbers for subgroups receiving anticoagulant therapy, but only for the actual periods of such therapy. Otherwise, the procedures used *in the refinement of the estimates* in stage two repeated those in stage one. These revised estimates were higher than the first set, but still probably slightly conservative, since stage two necessarily utilized for certain components the underestimates computed in stage one.

The total estimate of expected *additional* complications without anticoagulants was computed by the summation of these expected complications for the various age subgroups and deducting from the total the actual complications during the period of anticoagulant therapy. In this manner the *total saving from* the use of anticoagulants was estimated to be 12.9 complications, actually a small addition in relation to the total of 172 complications actually observed in the control group. For the various age subgroups, the savings from anticoagulants were assumed to be the numbers by which the complications as separately estimated for that subgroup exceeded the actual *complications* for the period in question. *Preparation* of separate estimates for most *other* subgroups by such elaborate *procedures* was not feasible. Therefore, at other points, *where* the tabulations required data "corrected *for*

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were transferred to the treated group for purposes of analysis, since this group was believed to be unselected (see Chapter III). Thus no estimates were needed for this group.

ceptions in treatment," the total of 12.9 mplications (or the total for given age oups), estimated as already described, was stributed to subgroups in the same proportions as actual complications were reported stributed. However, relatively more complex procedures were utilized at certain oints (notably, estimates for subgroups by me of occurrence) where the simpler ethod just described resulted in obvious istortion of subgroups.

ESTIMATES FOR DEATHS[b]

The subgroups derived from the foregoing stimates for complications, when rearanged, yielded estimates of the number of patients in each age group among the 35 who, without anticoagulants, would have developed a total of one, two, three, or four complications. These estimates were used in turn as the basis for the death estimates. It was assumed that if these cases had received no anticoagulants, they would have died at the rates that prevailed among control group cases having a similar total number of complications, receiving no anticoagulants at any time, and developing at least one complication outside the heart. Accordingly, these specific rates were applied to the appropriate subgroups among the 35 cases for whom exceptions were made. This procedure resulted in an estimate of deaths for this group, 7.5 deaths[a] higher than the actual number of deaths among these cases (namely, 6). It was assumed, therefore, that 7.5 deaths were prevented in the control group by the limited use of anticoagulants in certain cases after the development of complications. In other words, it was assumed that if no exceptions had been made, 103.5 deaths instead of the actual number, 96, would have occurred. In the computation of subcategories for data termed "corrected for exceptions in treatment," these estimated additional deaths were usually distributed to subgroups in the same proportions as actual deaths were distributed, the primary exception being the tables on time of death which required more precise estimating methods because exceptions in the administration of anticoagulants were usually made relatively late in the patient's illness.

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[b] Counts of bleeding episodes were also corrected for exceptions by the simple procedure described in footnote b, p 258.

[a] [illegible]
unc [illegible]
Du [illegible]
gor... was made proportionate to actual deaths.

APPENDIX C

Tests of Statistical Significance

THIS study deals with two samples drawn presumably from the same universe of cases hospitalized with coronary thrombosis with myocardial infarction. The method of selection was designed to randomize the selection of cases. By means of the odd- and even-day procedure, it was expected that two groups would be secured that, except for chance variations, would be alike in all relevant respects. The therapy received by the two groups was also intended to be similar, except for the administration of anticoagulant therapy to one of the two groups. When the clinical work was completed, an evaluation of the effects of anticoagulant therapy in coronary thrombosis was attempted by means of a statistical comparison of the developments experienced by the two groups during the first six weeks of their illness.[a]

Significance tests have been used in the interpretation of the observed differences since it is a well-known and familiar experience that two or more samplings from the same universe may, and probably will, differ by small or moderate amounts purely on a chance basis. Significance tests are useful in this connection since they describe for any particular set of data the extent to which given differences or variations may be expected on a chance basis alone. Thus they help one to evaluate the degree of confidence with which an initial hypothesis of no difference may be rejected as inconsistent with the findings.

The results of such tests are stated in terms of the number of times per 100 that differences as unusual as that observed can be expected to occur on a chance basis alone in an infinite number of pairs of samplings from the same universe or two identical universes. Limits are customarily set in advance as to how improbable an event must be on a chance basis before it is to be termed "statistically significant." After these limits are defined, differences are reported categorically as "significant" or "not significant."

To minimize the risk of terming a difference significant when it might be due to chance, the terms used in the text to describe significance levels have been defined conservatively as follows:

Category	*Times (per 100) differences as unusual as that observed can be expected to occur on a chance basis if true difference is zero*
Not statistically significant	Greater than 5 in 100
"Borderline" statistical significance	Between 1 and 5 in 100
Statistically significant	Less than 1 in 100 *but* at least 1 in 1000 or more
Highly significant statistically	Less than 1 in 1000

The dividing lines may also be referred to as "the one per cent level of significance," "the five per cent level of significance," etc., meaning that inferences made on this basis will be wrong on the average 1 or 5 times respectively in 100. The levels adopted differ to some extent from study to study according to the use to be made of the findings and the direction, therefore, in which it is most important to minimize the risk of a wrong decision.

[a] The grounds for pooling the data from different hospitals are outlined in footnote h, page 300.

In interpreting conclusions, one should note not only the significance categories reported, but also any accompanying statements indicating whether the difference was evaluated in one or both directions. Unless otherwise specified, all statements on statistical significance apply to the possibilities of a difference of a specified amount in *either* direction (two-tailed test). The probabilities of the occurrence of a given difference in one direction only are half those for the same difference in two directions. Therefore, if the reader wishes a less conservative evaluation of differences of these types, the stated probabilities of the occurrence in a given direction may be divided by 2 to secure a one-direction evaluation.

In the case of counts for deaths and those for number of complications, significance tests have been applied to differences in rates before correction for exceptions in treatment (for explanation of correction procedures, see Appendix B), since the application of significance tests to the corrected figures was considered questionable because of their artificial character. This limitation leads to unduly conservative results. There seemed to be no alternative, however, to the use of uncorrected rates since the corrected figures were estimates, prepared by means of logical assumptions from data for other untreated subgroups, and not direct observations, and since they included among their components data that did not conform to the principles of randomized sampling on which significance tests are based. Since no allowance for the decrease in deaths and complications in the control group due to exceptions in which anticoagulants were allowed was feasible in these tests, significance tests for deaths and complications necessarily understate the statistical significance of the differences associated with the use of anticoagulants.

The procedures applied in the actual significance tests necessarily differed according to the types of statistical measures to be compared, accepted technics for the evaluation of differences between two proportions being those most commonly employed. For such computations a knowledge of the magnitude of each of the proportions being tested is required, as well as the size of each of the two samples. A variation in any one of these four components alters the results. Tests for differences in other statistical measures usually involve also a standard deviation computed from distributions for the data being tested. For a description of the specific procedures involved in such tests, the reader is referred to standard statistical texts.[b]

The following technical details regarding the procedures utilized are added for the benefit of occasional specialized readers (others may skip items 1–5, listed in small type):

1. In significance tests involving *proportions*, the proportion characteristic of the total sample (control and treated groups combined) was used as the *estimate* of the universe proportion. Corrections for continuity were made wherever the significance class reported might be altered thereby.[c]

2. In instances where the total number of cases observed in any subgroup involved in a simple proportions test was less than 50, or the lowest expectation in any class was less than 5, the statistical significance of differences involving such groups was determined by methods appropriate for small samples, Table VIII of Fisher and Yates,[41] Mainland and Murray's tables,[138] or Fisher's[40] exact test being used as the data required.

3. Tests involving standardized rates were first performed in a preliminary exploratory manner, using test methods appropriate for unstandardized rates. Differences found to exceed one and one-half times their standard error were then retested, using the longer but more exact methods appropriate for differences between weighted rates before differences were reported as "significant" or "borderline."

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[b] Useful texts on elementary medical statistics include Hill[37] and Mainland.[138] Those in public health statistics and in general statistics are illustrated by Puffer[139] and Dixon and Massey[41] respectively. A full list would be too lengthy to cite.

[c] See Fisher[42] pp 92–91

4. Tests applied to differences between rates *stated in terms of average number per 100* (tests involving episode counts such as hemorrhages, which included more than one episode for some cases) used standard procedures for testing differences between means. Probabilities were assessed using Student's table for correcting probabilities corresponding to t when n exceeds 20, if this refinement could alter results.[d] The standard errors used were based routinely on observed frequency distributions.[e] Since these were typically nonnormal, approaching Poisson in shape, tests involving such data were limited to tests of the significance of differences between means (since such differences are symmetrically distributed and approach normality in form despite nonnormal distributions in original data).

5. Similar standard procedures were applied to tests involving differences between rates for the average number of given types of episodes per *1000 days observed, except that in these instances* the variances used were estimated from variances computed from case frequency distributions for the same data by multiplying these variances by the square of the correction factor needed to convert the average per case to the average number per 1000 days (i.e., the reciprocal of the mean days observed times 1000). The results (means, variances, and significance) are equivalent to those obtained by the following longer procedure: (1) computing separate day rates for each case, (2) weighting each individual case day rate by the ratio of the days observed for that case to the mean days observed for that group, (3) computing weighted means and weighted variances from these weighted individual rates, and (4) testing differences using usual standard procedures.

Because of the impossibility of applying the tests to data corrected for exceptions in *treatment*, the high significance level adopted, the use of two-tailed tests in most instances, and various conservative refinements applied in computations, the risk of considering anticoagulants influential in a given direction when differences are in reality chance phenomena is very low. On the other hand, the risk of considering anticoagulants (or other factors) not influential in some specific situation when they are actually influential is much greater. It is important to realize that anticoagulants (or other factors) may possibly be significant in the case of differences reported as of "borderline statistical significance" or "not statistically significant." The report "not statistically significant" simply means that significance was not proven at the significance level adopted. *It does not constitute positive proof of no difference.*

Moreover, the term "statistically significant" must be limited to its technical meaning. Differences may well be "statistically significant" that have no medical significance. Or, *vice versa*, differences not termed "statistically significant" might be medically significant, at least as clues or in individual cases. If there is, however, a *true* group difference in a measurable phenomenon, it should be possible, given a larger sample and more refined technics of experimentation or analysis, *to demonstrate* that such a difference is "statistically significant."

Interpretations of significance tests can *never be mechanical.* Likenesses may conceivably mask important but compensating differences and apparent differences may result from hidden uncontrolled factors rather than those specified in the classification. Normal selective processes and hidden defects in sampling, field reporting, measurement, classification can also give unsuspected and misleading results. Moreover, statistics describe *association*, and association, while a clue to causation in some instances, *does not itself* reveal the causative process. For a true understanding of the nature of revealed relationships, one must turn to the basic biological or other processes involved.

It was neither feasible nor appropriate that all the myriad differences reported be submitted to significance tests. In general, in comparisons not involving the composi-

[d] See Peters and VanVoorhis[184] pp. 171-176, 488-493.

[e] In order not to multiply unduly the number of published tables, only the more important of these distributions are reproduced in this report. Readers interested in other distributions can secure further details by writing the authors.

tion of the control and treated groups, the larger differences, when based on reasonably large samples, were selected for testing if they were potentially meaningful from a medical viewpoint. Those found statistically significant are stressed, or at least reported, in the text. Negative findings were used as a guide in writing but are not necessarily reported In tests of the comparability of the two samples, however, all results, both positive and negative, have been reported, the only criteria used in selecting topics to be tested or discussed being the availability of data and the importance of the topic.

As a special precaution against overreliance by the reader on untested differences based on small samples and subject inherently to wide chance fluctuations, all rates based on less than 30 cases are shown in all tables in italics, and no rates are reported in tables when the group used as a base includes only 10 cases or less. These limits are arbitrary and might well have been higher. Actually the size of the sample is only one of several variables important in determining statistical significance. In addition, special caution should be exercised in interpreting rates computed from proportions in which the numerator is 5 or less, regardless of the size of the denominator. Moreover, the smaller the difference—other factors being equal—the larger the samples that are required before differences between them can be considered other than chance phenomena.

APPENDIX D

The Clinical Use of Anticoagulants

I. DICUMAROL

In tablet or capsule form for oral use; each contains 25, 50, or 100 mg.

If feasible, as with an operative case, check prothrombin time before the first dose is given. In the event of an emergency following a thromboembolic episode, the first dose (usually 200 to 300 mg.) should be given and the prothrombin test completed within a few hours. This has been found to be acceptable because of the slow action of dicumarol, allowing plenty of time to counteract a high prothrombin time if present.

First and Second Phases

During the *first phase* of therapy (first one to three days), if very rapid anticoagulant action is desired, it is well to supplement dicumarol therapy with heparin until the prothrombin time reaches therapeutic levels (25 to 40 seconds). Prothrombin time tests should be taken every day through at least several weeks (the *second phase*) and the dosage of dicumarol should not be determined for that day until the report is back. Dosage for different individuals varies from 25 mg. every other day to 150 mg. a day.

Objective

For the *first* and *second phases* of treatment (through the fourth week after onset or after the last thromboembolic complication), if the control prothrombin time is between 12 and 18 seconds, the optimal therapeutic level should be between two and two and one-half times as long. For instance, in our laboratory the control level is 15 seconds ±1. We therefore consider the optimal therapeutic level to be between 25 and 40 seconds.

When the prothrombin time exceeds 35 seconds, no dicumarol is given until subsequent daily tests reveal it to be lower than 35 seconds, when another dose is given. If the rise has been rapid, the dosage thereafter should be relatively lower. If the patient proves to be fairly resistant to the drug, larger doses (e.g., 100–150 mg.) may be necessary.

The Third Phase—Long-term Dicumarol Therapy

At the conclusion of the second phase of dicumarol therapy lasting three to four weeks, a decision must be made regarding whether the treatment should be terminated or whether it is important for this patient to have the protection of anticoagulant therapy over a prolonged, perhaps indefinite period of time. This is determined on the basis of probable risk of recurring thromboembolic episodes, such as multiple emboli from a heart in auricular fibrillation, or recurrent thrombophlebitis.

In the event that long term therapy is decided upon, the prothrombin time tests may be taken at longer intervals up to one week apart for all except patients who are very difficult to control. The physician must plan the dosage schedule a week in advance.

Objective

To keep the prothrombin time between one and one-half and two times the normal control. Dosage may vary from 25 mg. every other day to 150 mg. a day.

Comment

Patients may be kept on this regimen for years (we have now followed some for seven or more years) without any damage to their liver, kidneys, or any other organs, and with increased protection against their thromboembolic condition. There is always *some* risk of hemorrhage, although when *properly* con-

trolled and watched by the physician, this is very low. It is nevertheless a calculated risk and must be weighed against the risk of their inherent disease.

II. STANDARDIZED PROCEDURES FOR THE USE OF HEPARIN BY PARTICIPATING HOSPITALS WHEN DESIRED (Exhibit)*

Heparin has been used by several of the participating hospitals during the initial phase of anticoagulant therapy before the prothrombin level has reached the therapeutic range from dicumarol administration. It has been pointed out that, while thromboembolic complications are rare during the first few days immediately following a fresh myocardial infarct, this may not be true for patients admitted later in the course of their disease. Where one or more complicating episodes have occurred, the desirability of obtaining more rapid anticoagulant action is evident. We have found that dicumarol in the dosage schedule recommended in the original instructions gives an effective therapeutic prothrombin level of 30 to 35 seconds by the third day in almost every patient It should, therefore, not be necessary to employ heparin longer than 24 to 48 hours if its use has been decided upon. When it is desired to use heparin, one of the following procedures should be utilized in this study for the purpose of standardization. The method used should be indicated clearly on the master forms when the case is reported

I. Intermittent Dose Method

1. An initial clotting time of the whole blood in glass tubes should be done before heparin is given. We recommend the Lee-White Modification of the Howell Method, which, although crude, still appears to be the most practical test."' It is performed as follows: "One ml. of blood is withdrawn from the arm vein, using a small all-glass syringe. The time at which the blood is drawn is noted. The needle is removed and the syringe them emptied into a small glass tube (Widal tube) about 8 mm. in diameter, which has previously been rinsed out with physiological saline solution (.85 per cent). The tube is rotated endwise (tilted) every 30 seconds and that point at which the blood no longer flows from its position, but maintains its surface contour when inverted, is taken as the endpoint. Care must be used to exclude air bubbles, as they tend to accelerate coagulation.... If the test is done at room temperature (65°-90°F.) the error, although present, is within one minute and may be neglected.... Normal coagulation time is 6½ minutes (5-8 minutes)." At present coagulation times should be done in glass tubes. In extensive tests at The New York Hospital on the clotting times of whole blood in paraffin-lined and lusteroid tubes, in untreated patients as well as in those receiving dicumarol, we have observed a wide range of variation in the clotting times in paraffin-lined and lusteroid tubes. This makes their use unsuitable for this study, and they are therefore not at present recommended (Vander Meer, R., Newman, A., and Wright, I. S.: Unpublished data). Further studies are being carried out.

2. 50 mg. of heparin in 50-100 ml. of physiological saline are then given slowly by vein. [*Fifty to 75 mg. of heparin in 15 cc. distilled water is now recommended.*]

3. Clotting times should be done 15 minutes and 2½ hours after the administration of heparin. If the clotting time at 2½ hours falls below 15 minutes, give 75 mg. of heparin for subsequent doses After a few trial studies the selected safe therapeutic dosage may be continued without repeating the clotting times routinely. The check of one series each day is a safety factor.

4. The dosage schedule may vary from

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* Current recommendations for the use of heparin ...

... complications are rare during first few days—see Tables 97, 98 and Appendix F Table 40.

patient to patient according to the clotting times. In general, injections of 50–75 mg. of heparin are given every three or four hours and continued for 2 days. [*At present, the most general use of heparin is during the first phase, or first one to three days of anticoagulant therapy, until the oral coumarin derivatives become effective. It is occasionally used one to four weeks (second phase) in place of the coumarin derivatives but is not practical for long-term therapy use.*] (This is the method used by the Swedish workers in a large series of cases of thrombophlebitis. The dosage recommended by them should not however be used in this country since the temporary International Standard for heparin, used in the United States, is 160% the strength of the Swedish standard heparin.)

5. The dicumarol dosage plan is the same whether or not heparin is used and 300 mg. should be given concurrently with the first dose of heparin. Prothrombin times should be done every day on blood taken just before a dose of heparin is due since large amounts of heparin in the circulating blood may affect the prothrombin determination.

II. Continuous Intravenous Drip Method

Some hospitals may prefer the continuous intravenous method to the multiple intravenous injection method. Accurate measurement of the prothrombin time to determine dicumarol dosage is impossible with this method because the heparin interferes with the coagulation of the plasma used in the test. If the continuous intravenous method is used, it has been recommended that 300 mg. of heparin be put in 1000 ml. of 5 per cent glucose and allowed to run in the vein at approximately 25 drops per minute for 24 hours. [*It is now recommended that 100 mg. heparin be added to 500 cc. distilled water. A 20–22 gauge needle should be fixed in the vein and the flow should be by slow drip, i.e., 10–15 drops per minute, more or less as needed, and for as long as heparin therapy is indicated.*] Clotting times should be done every 2 hours, otherwise trouble may be anticipated. The clotting time should be kept between 20 and 40 minutes. The total daily dosage necessary for this may vary considerably. The infusion needle should be firmly fixed in place. The veins of the backs of the hands or dorsal surfaces of the feet have been found to be the most satisfactory. Heparin given in this fashion may usually be discontinued after from 24 to 48 hours. Three hundred mg. of dicumarol may be given the first day. Four hours after the heparin infusion has been stopped, blood should be drawn for the prothrombin test and dicumarol dosage determined thereafter accordingly.

[*III. Heparin in Retarding Menstruum for Intramuscular Use: Check clotting time before administration. If normal, give 200 to 400 mg. intramuscularly, preferably in the outer upper quadrant of the buttocks. Check clotting time in 4, 8, and 12 hours. Do not give the next dose until the clotting time has shortened to less than three times the normal. Clotting time checks should be repeated before each successive dose which will average 12 to 24 hours apart if the response is satisfactory. The objective should be to obtain a prolongation of the clotting time two to four times with gradual return to normal in 12 to 24 hours.*

While this type of administration seems ideal in many respects, the response of the individual patient even to successive doses is not sufficiently predictable to be entirely satisfactory. It is fairly widely used as a preliminary treatment for dicumarol, Tromexan, or cyclocumarol, the first doses being administered simultaneously and the heparin being discontinued as the prothrombin time reaches therapeutic levels. It should be noted that a high concentration of heparin will cause a prolongation of the prothrombin time as well as the clotting time, though to a lesser degree. Therefore, blood for prothrombin tests should be drawn just before the next dose of heparin is due when the concentration is at the minimal level, rather than when it is high.]

May 19, 1947

III. TROMEXAN[b]

Dosage Schedule

Tablet form, 150 and 300 mg.

First phase (first through third day). The first dose is 1500 mg., unless the patient weighs more than 180 lb., when 1800 mg. may be given. A prothrombin test may be taken before or immediately after the first dose so that its effect may be counteracted if necessary. For immediate anticoagulant effect, heparin may be used for the first 24 hours, although this is not necessary in as many cases as with dicumarol because of the more rapid action of Tromexan. Daily prothrombin time tests are required to regulate dosage. Divided daily dosage is preferable with Tromexan. Average requirements run from 300 mg. to 900 mg. daily.

Objective

If the control prothrombin time is 12 to 18 seconds, the optimal therapeutic level is two to two and one-half times the control for the first and second phases (first four weeks of treatment).

Comments

Advantages of Tromexan are (1) rapid action (20 to 30 hours to therapeutic levels in most cases) and (2) rapid cessation of action on stopping the drug.

Disadvantages

Difficulty by some workers with control on a single-dose schedule. We have found divided-dose schedules overcome this to a large degree. The rapid responses to this drug make it a little more difficult than dicumarol for long-term therapy with some patients. On the other hand, with many patients, it is very satisfactory for long-term therapy.

[b] For a report on a clinical study of Tromexan, Appendix A.

IV. METHOD FOR THE DETERMINATION OF PROTHROMBIN CLOTTING TIME[c]

(Link and Shapiro Modification of Quick's Method)[d]

Method

All quantitative methods based on empirical rather than stoichiometric relationships can give reliable and reproducible results only by *strict conformity to rigidly* standardized manipulative conditions. This is *especially true* for the prothrombin time determinations, since one is dealing here with the sensitive and variable process of blood coagulation. If the procedure given *below is followed carefully*, reproducible results will be obtained.

Reagents and Solutions

1. *Sodium oxalate*, reagent grade, anhydrous. Prepare in a volumetric flask a 0.1 M. solution (13.4 grams *dissolved* in distilled water and made up to 1,000 ml.).

2. *Sodium chloride, reagent grade.* Prepare in a volumetric flask an 0.85 per cent *solution (8.5 grams dissolved in distilled* water and made up to 1,000 ml.).

3. *Calcium chloride, reagent grade*, anhydrous. Prepare in a volumetric flask 0.025 M. *solution (2.77 grams dissolved in* distilled water and made up to 1,000 ml.).

4. *Thromboplastin-calcium chloride suspension.* To 5.0 ml. of 0.85 per cent sodium *chloride solution in a 15 ml. centrifuge tube*, 0.1 grams of thromboplastin is added. The mixture is agitated thoroughly. *The temperature* of this suspension is maintained at 54 to 55 degrees C. in a water bath *for ten*

[c] References. Campbell *et al.*,[27] Overman, *Newman, and Wright*,[179] Quick,[193] Shapiro[179] and Shapiro *et al.*[22]

[d] As Brambel has stated,[30] the Quick prothrombin test does not measure prothrombin but rather a summation of the action of numerous factors. *Nevertheless*, it is a practical and useful guide to the effective control of anticoagulant therapy.

minutes with constant agitation, and then cooled to 25 to 26 degrees C. To the suspension, 5 ml. of 0.025 M., calcium chloride solution is added. The mixture is stirred for four minutes and centrifuged four minutes at 1,700 R.P.M. The centrifuge is brought to a standstill slowly so as to avoid resuspending the flocculent precipitate. The slightly turbid supernatant solution is removed with a pipet and used in the determination.

Procedure

To a test tube containing 0.5 ml. of 0.1 M. sodium oxalate solution, 4.5 ml. of freshly drawn blood is added. This is quickly mixed. The oxalated blood is centrifuged at 1,700 R.P.M. for ten minutes. The clear plasma is then transferred with a pipet to a test tube. The prothrombin time of the plasma should be determined as soon as possible after collection.

For the prothrombin time of whole plasma, approximately 0.5 ml. of plasma is transferred into a 75 x 10 mm. test tube. If diluted plasma is to be used, 0.1 ml. of plasma is transferred into another 75 x 10 mm. test tube and diluted with 0.85 per cent sodium chloride. To obtain a plasma concentration of 12.5 per cent, 0.1 ml. of plasma is diluted with 0.7 ml. of saline. The whole plasma and diluted plasma samples can be conveniently mixed by holding firmly the test tube near the top with the thumb and index finger, and striking the lower end sharply with glancing blows using the index finger of the other hand. This accomplishes a thorough mixing without contamination. The whole and diluted plasmas are mixed thoroughly and placed in the constant temperature water bath at 37 degrees C.

From the thromboplastin-calcium chloride suspension, 0.2 ml. is transferred into 100 x 12 mm. test tubes with a 0.2 ml. pipet (micro blood sugar). This suspension is blown into the test tubes and care is taken that the pipet is completely empty after each transfer. These tubes are placed in the rack beside the whole and diluted plasma samples in the constant temperature bath.

As soon as the contents of the tubes have reached the bath temperature, the prothrombin time of the plasma is determined as follows: The tube containing the whole plasma is shaken again, and 0.1 ml. is transferred with a 0.1 ml. pipet (micro blood sugar) to a tube containing 0.2 ml. of the thromboplastin-calcium chloride suspension. The plasma is blown quickly from the pipet and at the same time the stop watch is started (the stop watch can be conveniently operated by a foot treadle). The tube is tapped sharply to mix the solutions. This insures initiation of the clotting process uniformly throughout the solution. A small stirrer made of No. 22 Nichrome wire with a small loop on the end is then introduced. If any small droplets are present on the sides of the tube, they can be removed by passing the stirrer over them, thus making certain that all of the constituents are in the bottom of the tube. At this stage only two to three seconds should have elapsed since the time the plasma was added to the thrombo plastin-calcium chloride suspension.

The mixture is stirred so that the stirre loop sweeps across the test tube from one side to the other at a rate of two times per second. The end point (formation of clot) is that point at which the fibrin clot is sufficiently stable to be drawn to one side by the stirrer, thus bringing into view a clear area. The clot is usually somewhat turbid, since the calcium oxalate formed upon calcifying the oxal ted plasma is enmeshed in the clot. The formation of fibrids, which impart a viscous appearance to the solution before the clot forms, can be disregarded. Record the number of seconds required for clot formation. The same process is repeated using the diluted plasma.

Normal Standards:

Whole plasma	13 to 17 seconds
12.5 per cent dilution	35 to 52 seconds.

Schedule and Instructions (Exhibit)

1. NAME OF HOSPITAL ____________________

2. Case No. ____________
3. Treated case ☐ Control ☐
4. Age ____ 5. Sex ____ 6. Race ____

7. Name of patient ____________________
8. Hgt. ______ 9. Wgt. ______

10. Address ____________________
11. Build Lgt. ☐ Med. ☐ Heavy ☐

PREVIOUS HISTORY

12. Usual blood pressure, Systol. ________
diast. ________
13. Myocard. infarctions number ________
dates ________
14. Coronary disease Yes ☐ No ☐ Unk ☐
15. Congestive failure Yes ☐ No ☐ Unk ☐
16. Auricular fibrillation Yes ☐ No ☐ Unk ☐
17. Anginal syndrome Yes ☐ No ☐ Unk ☐
18. Other heart disease Yes ☐ No ☐ Unk ☐
19. Thrombophlebitis Yes ☐ No ☐ Unk ☐

20. Renal disease Yes ☐ No ☐ Unk ☐
21. Liver disease Yes ☐ No ☐ Unk ☐
22. Hemorrhagic tendencies Yes ☐ No ☐ Unk ☐
23. Arteriosclerosis Yes ☐ No ☐ Unk ☐
24. Hypertension Yes ☐ No ☐ Unk ☐
25. Cerebral accident Yes ☐ No ☐ Unk ☐
26. Diabetes mellitus Yes ☐ No ☐ Unk ☐
27. Gall bladder disease Yes ☐ No ☐ Unk ☐
28. Gout Yes ☐ No ☐ Unk ☐
29. Gangrene Yes ☐ No ☐ Unk ☐
30. Operation within 2 mo date ________ Yes ☐ No ☐ Unk ☐

Notes ____________________

PRESENT ILLNESS

31. Date onset ________

34. Date dicumarol discontinued ____________
35. Date admitted to hosp. ____________
36. Date disch from hosp ____________

SYMPTOMS

	1st week Dates From	1st week Dates To	1st week Degree 0-++++	2nd-6th week inc Dates From	2nd-6th week inc Dates To	2nd-6th week inc Degree 0-++++
37. Pain retrosternal.						
lt. shoulder, arm						
rt shoulder, arm						
neck						
back						
epigastric						
chest tightness						
38. Pericard friction rub						
39. Liver enlargement						
tenderness						
40. Dyspnoea						
41. Vomiting						
42. Edema, peripheral						
pulmonary						
43. Shock						

44. Cardiac enlargement: date 1st obs. ____________
duration ________ describe ________

45. Abnormal rhythms

Types (list)	Day 1st obs.	Duration (days)

46. E.C.G. Not done ☐ Dates done ________
a. Ant. infarct: New ☐ Old ☐ None ☐ Date ____
b. Post. infarct: New ☐ Old ☐ None ☐ Date ____
c. Sept. infarct: New ☐ Old ☐ None ☐ Date ____
d. Diffuse changes. New ☐ Old ☐ None ☐ Date ____
describe ____________

COMPLICATIONS

47. Pulm emboli: number ____________
48. Periph emboli: locations ____________ dates of occurrence ____________
dates of occurrence ____________
49. Cerebral emboli: number ____________
50. Periph ven. thromb locations ____________ dates of occurrence ____________
51. Myocard infarct., serial episodes primary area (dates) ____________ dates of occurrence ____________
(Exclude original infarct.)
52. Died date ________ other areas (dates) ____________
53. Autopsy Yes ☐ No ☐ cause of death a. primary ____________
b. contributing ____________

AUTOPSY FINDINGS (ATTACH COMPLETE PROTOCOL)

54. Coronary thrombosis acute Yes ☐ No ☐
chronic Yes ☐ No ☐
55. Myocardial infarction Yes ☐ No ☐
56. Mural thrombosis Yes ☐ No ☐
57. Venous thrombosis Yes ☐ No ☐

58. Pulmonary emboli Yes ☐ No ☐
59. Peripheral emboli Yes ☐ No ☐
60. Cerebral emboli Yes ☐ No ☐
61. Liver damage Yes ☐ No ☐
62. Unusual hemorrhage Yes ☐ No ☐

from onset		(Max.)	(Average)		Pulse (Max.)	Blood			Prothrombin				Treatment (enter total am't given in spec. time interval)				Transfusions	Remarks (Indicate hemorrhagic or thrombo-embolic complications, pertinent evidence, laboratory data, operations, other complications, etc.)
Day	Date		Sys.	Dias.		Leuc. (Max.)	Chol. (Max.)	Sed. (Max)	Undilute Seconds	Undilute Per Cent[b]	Dilute (Seconds)	Controls (Seconds[c])	Dicum.	Hepar	Vit.K	Xanth.	(Type, Am't)	
		63	64	65	66	67	68	69	70	70a	71	71a	72	73	74	75	76-7	78
1st																		
2																		
3																		
4																		
5																		
6																		
7																		
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34																		
35																		
36																		
37																		
38																		
39																		
40																		
41																		
42																		
4																		

Other drugs given. Total amount given in 6 weeks

atropine	________
papaverine	________
mercurial diuretics	________
salicylates	________
digitalis	________
other (specify below)	
________ . . .	. ________
________	________
________ . . .	. . ________
________ . . .	. ________
________	. . ________
________	. . ________
________ . .	. . ________

Fluids limited Yes ☐ No ☐
forced Yes ☐ No ☐
Sodium limited Yes ☐ No ☐
gm per 24 hrs. ________

. Oxygen therapy (describe) ________

. Method for prothrombin determination Quick ☐ Link-Shapiro ☐

. Reason for terminating dicumarol ________

____

5 If no dicumarol was given, state reason. ________

____

6. Private duty nurse? Yes ☐ No ☐ For how long ________

7 General appraisal of case: Severity at onset Mild ☐ Mod ☐ Severe ☐

Severity of course Mild ☐ Mod. ☐ Severe ☐

Date disch. from study ________

Condition on disch. ________

9 Signature of responsible investigator ________ Date ________

Explanatory Notes

SPECIFIC INSTRUCTIONS RELATING TO ITEMS ON FORM # 1:

Items 1–7: Self-explanatory

Items 8, 9, 11: Give height, weight and build of patient prior to this illness.

Items 10, 12: Self-explanatory

Items 13–30: (PREVIOUS HISTORY) Make an entry for every item:

a. Use the word "no" if a negative history is obtained. This does not mean that the patient could not have suffered from one of the diseases listed in a mild degree but for general purposes, the history was negative. In a few cases, the physical findings at the time of this examination will have to be taken into account—for example: if the patient shows marked arteriosclerosis as demonstrated by changes in the retina, it is to be assumed that the patient did have arteriosclerosis and it should be marked "yes" even though no specific complaints such as intermittent claudication has been present and even though no previous examination had made mention of this finding.

b. If "yes" is marked, list the specific items on which the diagnosis is made.

c. Mark "unk" (unknown) whenever it is impossible to obtain a reliable history. This may occur in a patient who comes in critically ill and could not be subjected to too much questioning or, for example, in a patient who is admitted and dies within a few hours.

For certain items detailed information listed below should be included:

Item 14: Coronary Disease—It could be assumed that many people after the age of 30 will have a certain degree of coronary disease. However, if "yes" is marked on this item, the patient should have had definite EKG findings or highly suggestive history of pain.

Item 18: Other Heart Disease—Classify according to "Nomenclature and Criteria for Diagnosis of Diseases of the Heart."

Item 20: Renal Disease—Include urinalysis, N.P.N., or urea-nitrogen. Note for both treated and control cases any renal disease which would be a contraindication to the use of dicumarol.

Item 21: Liver Disease—Include result of liver function tests, if done: serum protein, A/G ratio, icterus index. Note for both treated and control cases any liver disease which would be a contraindication to the use of dicumarol.

Item 22: Hemorrhagic Tendencies—Include, if significant, data on platelets, coagulation time, bleeding time, red blood cell fragility and capillary fragility. Note for both treated and control cases any hemorrhagic tendencies which would be a contraindication to the use of dicumarol.

Item 23: Arteriosclerosis—The diagnosis of arteriosclerosis will have to be viewed in the light of the present findings as to retinal arteries and peripheral vessels as well as the past history of intermittent claudication and other symptoms due to this disease.

Item 24: Hypertension—Include average blood pressure both systolic and diastolic.

Item 26: Diabetes—State whether or not insulin is being used and if diabetes has been well controlled.

Item 27: Gall Bladder Disease—If the patient gives a negative history, this question should be answered "no." It does not mean that a gall bladder function test need be done and found normal.

Item 28: Gout—Include uric acid level; state whether or not tophi are present.

Item 29: Gangrene—Specify location.

Item 30: Operation—State type of operation.

Item 31–36: (PRESENT ILLNESS) Describe only the episode of coronary occlusion and not some other illness which may have brought patient into hospital.

Items 37–45: (SYMPTOMS) Describe symptoms on which diagnosis of coronary occlusion was based. Make an entry for every item. If symptom was never present, record as 0 under degree, duration and date of onset.

Regarding data provided under Sections

37-45, we want information covering the entire six weeks of the survey, particularly in cases suffering complications. Since present plans call for a separate analysis of symptoms during the first week of the illness and those during later weeks, it is requested that if the symptoms listed in Items 37 through 45 of the form reappear in later weeks, these mptoms also be reported under Items 37 rough 45, together with the dates on which ey first appeared or recurred and the other formation specified in these items. These mptoms may recur particularly in connecon with complications and their reporting ill serve not only to facilitate a fuller description of the course of the illness, but also o confirm the diagnosis of the complications.

(REVISED REPORTING FORMS*—Revision of the forms used by the participating hospitals for reporting cases to the Central Laboratory has been extensive, but the general plan of the forms has not been altered. Among the more important changes is (Sections 37-43, present illness) addition of a second set of columns for the reporting of symptoms and signs which arise during the course of the illness in distinction to those present at onset.)

Item 37: Pain—Duration of Pain: If pain is intermittent state "yes"—give duration and add "int" behind the number of days.

Item 42: Edema—Pulmonary Edema: This term *does* not refer to a few crackling rales at the ...

of a ...

by r ...

It ...

seve ... azotemia occur, specify and record them ...

it ... may be several months or years previous to the present hospital admission. In this case, it would undoubtedly be due to a cardiac hypertrophy. In the rare case of acute cardiac dilatation the "date first observed" would most likely be a very recent date. Describe maximum apical impulse with reference to midsternal line and intercostal space; if there was x-ray, specify confirmation. Use criteria described in Ungerledier-Clark Table 1, p. 96, "*Nomenclature and Criteria for Diagnosis of Diseases of the Heart.*"

Item 46: Electrocardiograms—If EKG was done, make an entry for every line (a-d). If EKG was not done, these items need not be checked. Record dates on all EKG's done during entire hospital admission in the first line, writing in margin if necessary. In the following lines, a, b, c, record under "date" only the first EKG diagnosing the recent occlusion which led to the hospital admission. Coronary occlusions subsequent to the original coronary occlusion which led to the patient's hospitalization are recorded in Item 51. Under Item 46d, record first infarcts which are not anterior-apex, posterior-base, or septal. Under "describe," indicate briefly the evolutionary changes, and RT segment and T wave changes where the diagnosis is in doubt. Descriptions of diagnostic EKG findings should be entered in the space provided therefore under Item 46. The reason for this is that there is occasional difficulty in interpreting the brief data supplied in this section. This, we acknowledge, is in part due to this section being inadequately arranged. Another help in this connection would be for the reporter to write in "new" when he checks the appropriate location of the infarction.

(REVISED REPORTING FORMS—"Sections 46, EKG"—Addition of set of spaces for "New" infarcts.)

Item 47-53: (COMPLICATIONS) Make an entry for every item. Record "none" if complication did *not occur.*

Item 51: Myocardial Infarction, Serial Episodes—Note under "primary area" whether a propagation of the original coronary thromb...

this is ...

record ... other coronary occlusions occur-

* For explanation, see p. 15.

ring subsequent to the original occlusion for which the patient was admitted.

Item 54–62: (AUTOPSY FINDINGS)

Item 54: Coronary Thrombosis—"Acute" applies to fresh occlusions believed to have occurred during the present illness. "Chronic" applies to older occlusions.

Item 55: Myocardial Infarction—Applies to fresh infarcts occurring since hospitalization, or relevant to present illness. If old infarcted areas add "plus old" or "only old."

SPECIFIC INSTRUCTIONS RELATING TO ITEMS ON FORM #2[b]

Note: Name of patient, and case number, should be put on Form 2. The first day is considered to be the day of onset of coronary occlusion attack. This means that if a patient had an attack on March 1st and is not admitted to the hospital until the 4th, the spaces of 1st, 2nd, and 3rd days will remain blank.

Column "Interval from Onset": It is suggested that month number and day number be given following "1st day," "2nd day," or whichever day treatment or observation began, etc., thus: 3–27 for March 27. (This will clarify time relationships when dates are given for other items.)

Item 68: If cholesterol esters are obtained, they should be indicated in this column, using capital E after the figures.

Item 69: Sedimentation Rate—Indicate method, and normal value for that method in your laboratory.

Columns 70 and 71: Indicate *undilute* values for prothrombin times in seconds in Column 70. Indicate *dilute* values for prothrombin times in seconds, if these are being done, in Column 71. Give daily *standard* values for prothrombin times in Column 78 under "Remarks," or in Column 71 if this column is not used for dilute values: indicate at head of Column 71 whether it is used for dilute or for standard prothrombin times.

(Revised Reporting Forms—Columns 70–71, Prothrombin: Has been expanded into four columns as follows: "Undilute time in seconds," "Undilute time in per cent," "Dilute time," "Control time." Undiluted and diluted prothrombin times should be reported in seconds without any corrections or adjustments. *The column for per cent of prothrombin activity should be left blank* since percentages will be computed in the central office on a standard basis for each hospital.)

Item 72: Record total dose of dicumarol given at bottom of this column.

Item 75: Xanthines—Caffeine, if given, should be recorded here. Also theophylline, aminophyllin, etc. Specify what xanthines.

Item 76: Transfusions, Type: Type refers to whether blood or plasma and not to what blood type.

Column 78: This column is intended for remarks regarding significant findings such as hemorrhage, purpura, etc., and complications. Include such conditions as pulmonary edema, pulmonary infarct, etc. Any pertinent laboratory data considered significant not listed in Columns 63–77 should be recorded under "Remarks," Column 78.

The statistical analysis will cover a comprehensive analysis of deaths, thrombo-embolic episodes, and hemorrhagic manifestations occurring in all cases during the entire six-week period following the date of onset. Consequently, information covering the entire period is essential for every patient included in the study, whether a treated or a control case. This analysis will require a daily record of the prothrombin times and dicumarol dosage for *all* treated cases throughout the entire six-week period after onset covered by the study. Since the present form provides only for the reporting of maximum and minimum prothrombin time figures and the total weekly dosage of dicumarol after the end of the second week, it is requested that whenever the original case record permits, an additional supplemental daily record be submitted for each

[b] Includes last page of report form

treated case This supplemental report should specify the daily prothrombin time readings and the daily dicumarol and heparin dosage, and should cover, if feasible, all weeks not given in full on page 2 of the form and, as a minimum, at least the full period of dicumarol therapy.

If patients are discharged from the hospital prior to the end of the six-week period, please provide whenever possible a follow-up report as to the patient's condition at the end of the six-week period. This report should establish as a minimum: (1) whether the patient was or was not living at the end of the period, (2) whether the patient had developed any thromboembolic or hemorrhagic complications between the time of hospital discharge and the end of the six-week period, and (3) the dates of any deaths or complications These minimum facts should be supplemented by information as to the cause of any death occurring, the types and locations of any thromboembolic episodes, autopsy protocol findings, and other pertinent information as to the patient's condition.

(Revised Reporting Forms—On page 2 of the forms, a line has been provided for each day of the forty-two days (6 weeks) covered by the study.)

Item 79. For each drug, indicate the total amount given during 6-week period.

Item 82: Use of oxygen—Indicate number of days and whether a tent or other type of apparatus was used.

Item 84 Reason for termination of dicumarol therapy—Make entry for every treated case, e.g., "no further treatment needed by patient," "patient showed hemorrhagic tendencies," etc.

Item 85: Reason no dicumarol was given —Make an entry for every case, e g., "control case," "contraindicated because of liver disease," "died before therapy could be started," etc.

Item 87: Give your appraisal of the case as to the severity at the onset and during the course of the disease. *Date of discharge* does not mean discharge from hospital but refers to date at end of *6 weeks* following date of diagnosis, at which time the period of observation for this study terminates; *Condition on discharge* refers to date explained above.

(Revised Reporting Forms—A new section has been added on the reverse of Page 2, entitled "Explanatory Notes" and is intended for additional descriptive material pertaining to any statement for which there is inadequate space in the body of the form. Any complication, for example, for which space 78 does not provide sufficient space can be discussed in this additional section.)

There should be some statement entered under every numerical subdivision on the two sheets of the reporting form. When a space remains blank, the Central Laboratory does not know whether a negative report is intended, whether the answer is unknown, or whether the particular item was overlooked by the man filling out the report. Thus, "no," "none," or "0," and "unknown" are desired. This is applicable at present particularly to the section on "previous history."

ring subsequent to the original occlusion for which the patient was admitted.

Item 54–62: (AUTOPSY FINDINGS)

Item 54: Coronary Thrombosis—"Acute" applies to fresh occlusions believed to have occurred during the present illness. "Chronic" applies to older occlusions.

Item 55: Myocardial Infarction—Applies to fresh infarcts occurring since hospitalization, or relevant to present illness. If old infarcted areas add "plus old" or "only old."

SPECIFIC INSTRUCTIONS RELATING TO ITEMS ON FORM #2[b]

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Column "Interval from Onset": It is suggested that month number and day number be given following "1st day," "2nd day," or whichever day treatment or observation began, etc., thus: 3–27 for March 27. (This will clarify time relationships when dates are given for other items.)

Item 68: If cholesterol esters are obtained, they should be indicated in this column, using capital E after the figures.

Item 69: Sedimentation Rate—Indicate method, and normal value for that method in your laboratory.

Columns 70 and 71: Indicate *undilute* values for prothrombin times in seconds in Column 70. Indicate *dilute* values for prothrombin times in seconds, if these are being done, in Column 71. Give daily *standard* values for prothrombin times in Column 78 under "Remarks," or in Column 71 if this column is not used for dilute values: indicate at head of Column 71 whether it is used for dilute or for standard prothrombin times.

[b] Includes last page of report form

(Revised Reporting Forms—Columns 70–71, Prothrombin: Has been expanded into four columns as follows: "Undilute time in seconds," "Undilute time in per cent," "Dilute time," "Control time." Undiluted and diluted prothrombin times should be reported in seconds without any corrections or adjustments. *The column for per cent of prothrombin activity should be left blank* since percentages will be computed in the central office on a standard basis for each hospital.)

Item 72: Record total dose of dicumarol given at bottom of this column.

Item 75: Xanthines—Caffeine, if given, should be recorded here. Also theophylline, aminophyllin, etc. Specify what xanthines

Item 76: Transfusions, Type: Type refers to whether blood or plasma and not to what blood type.

Column 78: This column is intended for remarks regarding significant findings such as hemorrhage, purpura, etc., and complications. Include such conditions as pulmonary edema, pulmonary infarct, etc. Any pertinent laboratory data considered significant not listed in Columns 63–77 should be recorded under "Remarks," Column 78.

The statistical analysis will cover a comprehensive analysis of deaths, thromboembolic episodes, and hemorrhagic manifestations occurring in all cases during the entire six-week period following the date of onset. Consequently, information covering the entire period is essential for every patient included in the study, whether a treated or a control case. This analysis will require a daily record of the prothrombin times and dicumarol dosage for *all* treated cases throughout the entire six-week period after onset covered by the study. Since the present form provides only for the reporting of maximum and minimum prothrombin time figures and the total weekly dosage of dicumarol after the end of the second week, it is requested that whenever the original case record permits, an additional supplemental daily record be submitted for each

Explanation of Exception and Disposition[a]	Number of Cases
ases Admitted on Even Days—	
Receiving no anticoagulants initially but placed on anticoagulants eventually after the development of a thromboembolic complication	
Reasons for giving[b],	
Following venous thrombosis (thrombophlebitis or phlebothrombosis)........	12
Following pulmonary embolism ..	12
Following peripheral embolism	7
Following cerebral embolism	3
Following extension of a myocardial infarction	1
Total cases in subgroup.....	35[c]
Disposition. Retained in control group and *estimates* prepared of complications and deaths prevented by use of anticoagulants	
Receiving anticoagulants for miscellaneous reasons in the absence of thromboembolic complications	
Reasons for giving:	
Request of private physician	14
Case treated with anticoagulants by error. . .	4
No reason given	3
Suspected venous thrombosis, eventually ruled out	2
Polycythemia vera.	1
Patient an employee of the hospital	2
Initial diagnosis pulmonary embolism, correct diagnosis not made until 4th day, anticoagulants begun for pulmonary embolism continued. ..	1
Patient developed symptoms following exercise tolerance test, anticoagulants given to determine effect on fresh occlusion .	1
Severity of case, total	2
Heparin given for progressive gangrene in desperate case	
Dicumarol given because of septal involvement and severity of case on advice of consultant	
Patient treated with dicumarol for previous myocardial infarction	1
Total cases in subgroup ..	31[d]
Disposition. Shifted to treated group	

[a] For explanation of logic of disposition of exceptions, see pp. 20–23 of the text.

[b] Listed according to the last complication prior to the institution of anticoagulant therapy.

[c] Of these 35 cases, 22 received anticoagulants after their first complication, 9 after their second, 3 after their third, and 1 received anticoagulants only after his fourth complication.

[d] No patient in this group developed a thromboembolic complication for at least two days following the initiation of anticoagulant therapy and most patients did not develop any complication.

APPENDIX F

Supplementary Statistical Tables

APPENDIX TABLE 1

EXCEPTIONS IN ANTICOAGULANT THERAPY: *Reasons for Exceptions* and Number and Disposition of Cases in Which Exceptions Were Made in Use of Anticoagulants according to Prescribed Odd- and Even-Day *Procedure*

Explanation of Exception and Disposition*	Number of Cases
Cases Admitted on Odd Days—	
Receiving no anticoagulants for miscellaneous reasons	
Reasons for withholding:	
Anticoagulants omitted at request of private physician.	5
Patient refused venipuncture after 1 dose of dicumarol. . . .	1
Tardy diagnosis of coronary occlusion with myocardial infarction, total	4
Case who entered with ventricular lar tachycardia, cause debated. Diagnosis eventually made.	
Case with initial diagnosis of bowel obstruction, diagnosis of coronary occlusion made on 2nd day, patient died on 3rd day.	
Case originally surgical admission, diagnosis of coronary occlusion made late.	
Case where diagnosis of coronary occlusion was not made until 15th day.	
Patient admitted near midnight and thought to be even-day case until discharge.. . ..	1
Initial diagnosis of cerebrovascular accident, later decided to be cerebral angiospasm. .	1
Total cases in subgroup.. .	12
Disposition: Shifted to control group	
Receiving no anticoagulants because of medical contraindications	
Reasons for withholding:	
Hemorrhage or hemorrhagic state, total................	5
Case with hemorrhagic tendency, type not specified.	
Case with hematemesis, etiology undetermined, on entry.	
Case with hematemesis and melena, etiology undetermined.	
Case with profuse hemorrhage from peptic ulcer.	
Case with acute gastric dilatation with hemorrhage.	
Cancer of lungs with pleural metastases	1
Prolonged prothrombin time (impaired prothrombin activity) upon admission, total......	3
Case with prolonged *initial* prothrombin time, liver disease *suspected, but not* proved.	
Case with prolonged initial prothrombin time, presumably due to malnutrition.	
Case with prolonged initial prothrombin time, albuminuria, possible liver insufficiency.	
Complex cases with variety of factors felt to be contraindications to anticoagulant therapy, total...	3
Post-operative case with congestive heart failure, anemia, hematuria, and albuminuria with elevated NPN, chills, and fever	
Case *in poor* general condition and progressive downhill course in patient suspected of having both renal and liver disease	
Case with prolonged initial *prothrombin* time; liver disease manifested by hepatomegaly, *slightly* abnormal liver function tests; renal disease manifested by mild albuminuria and cylindruria, elevated NPN and blood creatinine.	
Total cases in subgroup... .	12
Diposition: Retained in treated group	

APPENDIX TABLE 3

AND SEX COMPOSITION OF THE SAMPLE, BY FIVE-YEAR AGE GROUPS. Number of Cases in the Total Sample and the Control and Treated Groups, by Sex and Five-Year Age Groups

Age	Number of Cases[a]								
	Total Sample			Control Group			Treated Group		
	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females
20–24	1	1	—	—	—	—	1	1	—
25–29	—	—	—	—	—	—	—	—	—
30–34	3	3	—	1	1	—	2	2	—
35–39	22	21	1	8	8	—	14	13	1
40–44	52	46	6	25	23	2	27	23	4
45–49	114	99	15	47	40	7	67	59	8
50–54	145	129	16	48	41	7	97	88	9
55–59	225	184	41	104	83	21	121	101	20
60–64	168	118	50	71	57	14	97	61	36
65–69	137	88	49	62	40	22	75	48	27
70–74	99	67	32	53	38	15	46	29	17
75–79	43	23	20	17	10	7	26	13	13
80–84	16	6	10	4	3	1	12	3	9
85–89	3	3	—	1	1	—	2	2	—
Age unknown	3	1	2	1	1	—	2	—	2
Total cases	1031	789	242	442	346	96	589	443	146

[a] For definition of a "case" see footnote a, Table 3 of text.

APPENDIX TABLE 2

EFFECT OF VARIOUS METHODS OF HANDLING EXCEPTIONS IN TREATMENT: Exhibit Showing the Effects on the Major Findings of Various Methods of Handling Exceptions in Treatment

Method of Analysis	Total Number of Cases in Sample	Deaths in Total Six-Week Period: Number	Deaths in Total Six-Week Period: Per-cent	Thromboembolic Complications in Total Six-Week Period: Cases Developing Complications: Number	Cases Developing Complications: Per cent	Number of Complications: Number	Number of Complications: Per 100 Cases	Hemorrhages Due to, or Aggravated by, Anticoagulants: Number Reported	Average Number per 100 Cases
Method 1[a]:									
Pure odd-even day assignment regardless of treatment									
"Control" group thus defined	461	100	21.7	116	25.2	173	37.5	9	2 0
"Treated" group thus defined	570	90	15 8	63	11.1	76	13 3	50	8 8
Method 2[b]:									
Pure treatment categories regardless of day of admission									
"Control" group thus defined	419	96	22.9	83	19.8	113	27.0	—	—
"Treated" group thus defined	612	94	15.3	96	15 7	136	22.2	59	9 6
Method 3[c]:									
All exceptions entirely omitted from sample									
"Control" group thus defined	395	88	22.3	77	19.5	104	26 3	—	—
"Treated" group thus defined	546	82	15.0	57	10.4	67	12.3	50	9 2
Method 4[d]:									
Method actually used (i.e., Method 1—where exceptions were for reasons related to outcomes—plus corrections for exceptions; Method 2—where exceptions were for reasons unrelated to outcomes)									
"Control" group thus defined									
Rates based on numbers as reported	442	96	21 7	115	26.0	172	38 9	5	1.1
Rates corrected for exceptions in treatment	442	103 5	23.4	115	26 0	184.9	41.8	—	—
"Treated" group thus defined	589	94	16 0	64	10 9	77	13.1	54	9 2

[a] This method retains original randomness of assignment of cases to treatment groups (insofar as odd-even day classification permits) but retains all the impurities in treatment that actually occurred

[b] This method introduces an obvious bias in prognosis between the two groups since some of the [illegible] as an exception and under this procedure such cases are [illegible] the control group but their [illegible]

[c] [illegible] of treatment categories by sacrificing equality of prognosis because [illegible]

[d] This procedure switched cases when the exceptions appeared to have [illegible] correlated with the outcomes under study and retained in the original odd or even-day groups cases in [illegible] outcomes under study [illegible] consistent with retaining approximate comparability in prognosis. Statistical adjustment [illegible] used to correct for the remaining impurities in treatment classifications. It is a compromise between Method 1 and Method 2 above.

APPENDIX TABLE 5

PREVIOUS CORONARY ARTERY DISEASE AND USUAL PREVIOUS BLOOD PRESSURES IN THE CONTROL AND TREATED GROUPS: Number of Cases in the Control and Treated Groups with any Clinical Evidence of Previous Coronary Artery Disease and/or with Usual Previous Blood Pressures in the Hypertensive Range, by Age

Status of Condition	Number of Cases															
	Control Group								Treated Group							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown	All Ages	Under 40	40-49	50-59	60-69	70-79	80-87	Age Unknown
Previous Coronary Disease (Any Clinical Evidence of)[a]																
nt	269	7	34	101	85	38	4	—	334	8	47	121	105	41	7	2
present	139	2	35	43	38	21	—	—	209	9	39	86	48	21	6	—
eterminate . . .	34	—	3	8	10	11	1	1	46	—	8	11	19	7	1	—
otal cases .	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2
Usual Previous Blood Pressure[b]																
rmal or below	151	5	30	54	36	24	2	—	221	9	36	82	64	24	5	1
pertensive . .	131	2	16	45	44	23	1	—	175	1	24	60	61	21	7	1
report	160	2	26	53	53	23	2	1	193	7	34	76	47	27	2	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2

[a] For definition of previous coronary disease, see footnote a, Table 15 of the text.
[b] For definition of blood pressure categories, see footnotes a and b, Table 19 of the text.

APPENDIX TABLE 4

OVERWEIGHT AND UNDERWEIGHT IN THE CONTROL AND TREATED GROUPS: *Number of Cases Overweight, within Normal Range, and Underweight in the Control and Treated Groups, by Age*

Degree of Overweight or Underweight[a]	Number of Cases															
	Control Group								Treated Group							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
30% or more overweight	6	—	1	5	—	—	—	—	18	—	6	7	5	—	—	—
20-29% overweight	18	—	2	4	9	2	1	—	22	2	4	10	3	3	—	—
10-19% overweight	44	—	9	18	12	5	—	—	50	1	9	21	18	1	—	—
Total 10% or more overweight	68	—	12	27	21	7	1	—	90	3	19	38	26	4	—	—
Less than 10% overweight[b]	71	1	14	26	24	6	—	—	123	4	18	51	36	13	1	—
Less than 10% underweight	93	1	15	30	33	13	1	—	116	4	19	39	34	18	2	—
Total within normal weight range	164	2	29	56	57	19	1	—	239	8	37	90	70	31	3	—
10-19% underweight	44	2	3	15	10	13	1	—	61	2	4	25	20	8	2	—
20-29% underweight	13	—	1	2	5	5	—	—	22	—	2	8	7	3	2	—
30% or more underweight	4	—	—	—	2	2	—	—	1	—	—	1	—	—	—	—
Total 10% or more underweight	61	2	4	17	17	20	1	—	84	2	6	34	27	11	4	—
Weight unknown	149	5	27	52	38	24	2	1	176	4	32	56	49	26	7	2
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2

[a] For method of computation, see *footnote a, Table 11 of text.*

[b] Seventeen cases with weights exactly equal to standard weights are included here.

APPENDIX TABLE 7

EGREE OF PAIN AND DYSPNEA, BY AGE AND TREATMENT GROUPS: Number of Cases in the Control and Treated Groups Experiencing Maximum Pain and Dyspnea of Various Degrees during the Six-Week Period of Observation, by Age and Treatment Groups

aximum Degree of Condition Reported at Any Time	Number of Cases[a]															
	Control Group								Treated Group							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
Pain[b]																
o pain	17	—	1	4	7	5	—	—	21	—	4	4	5	7	1	—
ne degree of pain	11	—	1	4	3	3	—	—	10	—	1	5	3	1	—	—
wo degrees of pain	79	1	11	26	28	12	1	—	102	4	13	30	31	15	2	1
hree degrees of pain	181	4	32	66	49	29	1	—	231	7	31	95	68	26	3	1
our degrees of pain	150	4	26	51	44	21	3	1	220	6	45	77	62	23	7	—
egree of pain unknown	3	—	1	—	2	—	—	—	5	—	—	1	3	—	1	—
o report on pain	1	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2
Dyspnea																
o dyspnea	201	4	36	79	54	25	2	1	307	10	54	116	88	33	5	1
ne degree of dyspnea	44	1	8	18	10	7	—	—	63	1	8	28	18	6	2	—
wo degrees of dyspnea	89	2	14	27	31	14	1	—	112	5	15	42	32	13	4	1
hree degrees of dyspnea	57	1	9	13	19	13	2	—	58	—	9	16	18	13	2	—
our degrees of dyspnea	33	1	3	10	11	8	—	—	32	1	5	13	10	3	—	—
egree of dyspnea unknown	12	—	2	4	4	2	—	—	14	—	3	2	6	2	1	—
o report on dyspnea	6	—	—	1	4	1	—	—	3	—	—	1	—	2	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2

[a] For percentage of cases with a known record in the total sample in each category, see Tables 34 and 38 of the text. Percentages for selected components also appear in Tables 31, 33, 35, and 37.

[b] For types of pain included, see footnote a, Table 34 of the text

APPENDIX TABLE 6

PREVIOUS DIABETES, BY AGE AND SEX: *Number and Percentage of Both Sexes and of Males and Females in the Control and Treated Groups Reported to Have Shown Diabetes in Their Medical Histories*

Status of Diabetes in History	Control Group								Treated Group							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
	Number of Cases															
Diabetes present																
Males ..	29	—	2	11	8	8	—	—	26	1	2	12	7	4	—	—
Females	22	—	1	4	12	5	—	—	36	—	1	8	18	7	2	—
Both sexes .	51	—	3	15	20	13	—	—	62	1	3	20	25	11	2	—
Total cases whose history in regard to diabetes was known																
Males .	340	9	62	123	96	45	4	1	434	16	82	187	*104*	*40*	5	—
Females	95	—	9	28	35	22	1	—	145	1	12	29	63	30	8	2
Both sexes	*435*	*9*	*71*	*151*	*131*	*67*	*5*	*1*	*579*	*17*	*94*	*216*	167	70	13	2
	Percentage of Cases[a] with a History of Diabetes															
Diabetes present																
Males .	9	—[b]	3	8	8	18	—[b]	—[b]	6	*6*	2	6	7	10	—[b]	—[b]
Females	23	—[b]	—[b]	*14*	34	*25*	—[b]	—[b]	25	—[b]	*8*	*28*	29	23	—[b]	—[b]
Both sexes .	12	—[b]	4	10	15	19	—[b]	—[b]	11	*6*	3	9	15	16	*15*	—[b]

Note: *Italics are used when percentages quoted have less than 50 cases as a base since chance factors render such rates particularly unstable.*

[a] Based on total number of cases whose history in regard to diabetes was known

[b] Not computed since there were less than 10 cases in the sample.

APPENDIX TABLE 7

DEGREE OF PAIN AND DYSPNEA, BY AGE AND TREATMENT GROUPS: Number of Cases in the Control and Treated Groups Experiencing Maximum Pain and Dyspnea of Various Degrees during the Six-Week Period of Observation, by Age and Treatment Groups

Maximum Degree of Condition Reported at Any Time	Number of Cases[a]															
	Control Group								Treated Group							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
Pain[b]																
No pain	17	—	1	4	7	5	—	—	21	—	4	4	5	7	1	—
One degree of pain	11	—	1	4	3	3	—	—	10	—	1	5	3	1	—	—
Two degrees of pain	79	1	11	26	28	12	1	—	102	4	13	36	31	15	2	1
Three degrees of pain	181	4	32	66	49	29	1	—	231	7	31	95	68	26	3	1
Four degrees of pain	150	4	26	51	44	21	3	1	220	6	45	77	62	23	7	—
Degree of pain unknown	3	—	1	—	2	—	—	—	5	—	—	1	3	—	1	—
No report on pain	1	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2
Dyspnea																
No dyspnea	201	4	36	79	54	25	2	1	307	10	54	116	88	33	5	1
One degree of dyspnea	44	1	8	18	10	7	—	—	63	1	8	28	18	6	2	—
Two degrees of dyspnea	89	2	14	27	31	14	1	—	112	5	15	42	32	13	4	1
Three degrees of dyspnea	57	1	9	13	19	13	2	—	58	—	9	16	18	13	2	—
Four degrees of dyspnea	33	1	3	10	11	8	—	—	32	1	5	13	10	3	—	—
Degree of dyspnea unknown	12	—	2	4	4	2	—	—	14	—	3	2	6	2	1	—
No report on dyspnea	6	—	—	1	4	1	—	—	3	—	—	1	—	2	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2

[a] For percentage of cases with a known record in the total sample in each category, see Tables 34 and 38 of the text. Percentages for selected components also appear in Tables 31, 33, 35, and 37.

[b] For types of pain included, see footnote a, Table 34 of the text.

APPENDIX TABLE 8

DEGREE OF PAIN AND DYSPNEA, BY PERIOD OF ILLNESS: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Experiencing Maximum Pain and Dyspnea of Various Degrees during the First Week and from the Second through the Sixth Week of Observation

Period and Maximum Degree of Condition Reported[a]	Pain[b]						Dyspnea					
	Number of Cases			Percentage of Cases[c]			Number of Cases			Percentage of Cases[c]		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
First week:												
One degree	21	10	11	2	2	2	106	43	63	10	10	11
Two degrees	184	81	103	18	18	17	199	86	113	20	20	19
Three degrees	407	180	227	39	41	39	108	53	55	11	12	10
Four degrees	368	148	220	36	34	37	55	28	27	5	6	5
Degree unknown	8	3	5	1	1	1	25	11	14	2	3	2
Total with symptoms	988	422	566	96	96	96	493	221	272	48	51	47
Total with report on symptoms	1029	441	588	100	100	100	1030	436	584	100	100	100
Total cases at beginning of the period	1031	442	589	—	—	—	1031	442	589	—	—	—
Second through sixth week:												
One degree	28	11	17	3	3	3	27	12	15	3	3	3
Two degrees	37	13	24	4	3	5	16	9	7	2	2	1
Three degrees	23	10	13	2	3	2	16	10	6	2	3	1
Four degrees	7	5	2	1	1	—[d]	15	8	7	1	2	1
Degree unknown	89	48	41	10	12	8	47	24	23	5	6	5
Total with symptoms	184	87	97	20	22	18	121	63	58	13	16	11
Total with report on symptoms	938	401	537	100	100	100	936	399	537	100	100	100
Total cases at beginning of the period	959	410	549	—	—	—	959	410	549	—	—	—

[a] Symptoms for the second through the sixth week were probably underreported to a greater extent than indicated.

[b] For definition of types of pain included, see footnote a of Table 33 of the text.

[c] Based on number of cases with a report on condition

[d] Less than .5 of 1 per cent

APPENDIX TABLE 9

OCCURRENCE OF VOMITING AND FRICTION RUB: Number of Cases in the Control and Treated Groups Developing Vomiting and a Recognized Pericardial Friction Rub during the Six-Week Period of Observation, by Age

Status of Condition	Number of Cases[a]															
	Control Group								Treated Group							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
Vomiting																
Present	137	3	23	48	43	18	2	—	169	3	24	62	52	23	4	1
Not present	300	6	49	102	88	51	3	1	418	14	70	156	120	47	10	1
Status unknown	5	—	—	2	2	1	—	—	2	—	—	—	—	2	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2
Friction Rub																
Present	60	2	7	21	18	11	1	—	89	4	12	34	28	8	3	—
Not present	377	7	65	127	114	59	4	1	490	13	82	182	140	60	11	2
Status unknown	5	—	—	4	1	—	—	—	10	—	—	2	4	4	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2

[a] For percentages with a known record with condition present, see Tables 39 and 42 of the text.

APPENDIX TABLE 10

TIME OF FIRST VOMITING: Number of Cases in the Total Sample and in the Control and Treated Groups Vomiting for the First Time on *Various Days of the Six-Week Period of Their Illness*

Status of Vomiting and Day of Illness First Occurred	Number of Cases		
	Total Sample	Control Group	Treated Group
Vomiting present; first occurred:[a]			
1st day	218	93	125
2nd day	48	20	28
3rd day	8	6	2
4th day	10	8	2
5th day	7	3	4
6th day	4	1	3
7th day	—	—	—
8th day	2	2	—
9th day	—	—	—
10th day	2	—	2
After 10th day	4	3	1
Day unknown	3	1	2
Total developing vomiting[b]	306	137	169
No vomiting	718	300	418
No report on vomiting	7	5	2
Total cases	1031	442	589
Total vomiting in first week[c]	296	132	164
Total vomiting in second through sixth week[d]	14	9	5

[a] Cases are classified according to the day of their illness on which vomiting occurred for the first time. It may have reappeared at a later day Four control cases and two treated cases developed vomiting a second time after this symptom had cleared up.

[b] For age breakdown of cases experiencing *vomiting, see Appendix* Table 9.

[c] Total vomiting in first week includes one case known to have vomited in the first week, but on an unknown day of this week

[d] Total vomiting in the second through the sixth week includes cases not reported on a daily basis for this period because they were second episodes of vomiting.

APPENDIX TABLE 11

TIME OF RECOGNITION OF FRICTION RUB: *Number of Cases in the Total Sample and* in the Control and Treated Groups Developing a Recognized Pericardial Friction Rub for the First Time on Various Days of the Six-Week Period of Their Illness

Status of Friction Rub and Day of Illness First Recognized	Number of Cases		
	Total Sample	Control Group	Treated Group
Friction rub recognized; first observed:[a]			
1st day	10	4	6
2nd day	27	12	15
3rd day	30	12	18
4th day	24	7	17
5th day	20	10	10
6th day	12	3	9
7th day	6	2	4
8th day	3	1	2
9th day	4	1	3
10th day	3	2	1
After 10th day	10	6	4
Total with recognized rub[b]	149	60	89
Friction rub never recognized	867	377	490
Status indeterminate	15	5	10
Total cases	1031	442	589

[a] Cases are classified according to the day of their illness on which friction rub was first observed It may have been present earlier, but not *have been observed*. Moreover, it may have reappeared at a later date. In two treated cases and three control cases such reappearances were reported.

[b] For age breakdown of total cases experiencing friction rub, see Appendix Table 9

APPENDIX TABLE 12

... and Percentage of Cases in the Total
... Recognized Cardiac Enlargement
... ta by Age for the Total Sample

Status in Regard to Cardiac Enlargement	Number of Cases										Percentage of Cases*									
	Total Sample								Control Group	Treated Group	Total Sample								Control Group	Treated Group
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown	All Ages	All Ages	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown	All Ages	All Ages
None observed	529	19	119	193	143	46	7	2	208	321	53	79	74	53	48	34	—	—[b]	49	56
Cardiac enlargement present and first observed																				
Prior to illness	81	2	5	27	29	15	2	1	42	39	8	8	3	7	10	11	*11*	—[b]	10	7
During 1st week	328	3	30	118	103	66	8	—	147	181	33	*13*	19	33	35	47	*42*	—[b]	35	31
During 2nd through 6th week	58	—	7	23	13	8	2	—	26	32	6	—	4	6	6	6	*11*	—[b]	6	5
Present, date first observed not given	5	—	—	3	2	—	—	—	1	4	—[a]	—	—	1	1	—	—	—[b]	—[a]	1
Total with enlargement	472	5	42	171	152	89	12	1	216	256	47	*21*	26	47	52	66	*65*	—[b]	51	*44*
Total with report on enlargement	1001	24	161	364	295	135	19	3	424	577	100	*100*	100	100	100	100	*100*	—[b]	100	100
Total cases	1031	26	166	370	303	142	19	3	442	559	—	—	—	—	—	—	—	—	—	—

APPENDIX TABLE 13

DEGREE OF PULMONARY EDEMA, LIVER ENLARGEMENT, AND PERIPHERAL EDEMA, BY AGE AND TREATMENT GROUPS: Number of Cases in the Control and Treated Groups Showing Maximum Pulmonary Edema, Liver Enlargement, and Peripheral Edema of Various Degrees during the Six-Week Period of Observation, by Age and Treatment Groups

Maximum Degree of Condition Reported at Any Time	Number of Cases*															
	Control Group								Treated Group							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
Pulmonary Edema																
No edema	303	7	58	111	88	36	2	1	440	17	79	162	124	45	11	2
One degree of edema	43	1	8	14	12	6	2	—	41	—	4	18	9	9	1	—
Two degrees of edema	52	1	5	13	19	14	—	—	52	—	5	25	15	7	—	—
Three degrees of edema	21	—	1	9	4	9	1	—	26	—	4	5	13	2	2	—
Four degrees of edema	14	—	—	4	6	4	—	—	16	—	1	5	6	4	—	—
Degree of edema unknown	3	—	—	1	1	1	—	—	7	—	—	1	4	2	—	—
No report on edema	3	—	—	—	3	—	—	—	7	—	1	2	1	3	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2
Liver Enlargement																
No enlargement	350	8	68	123	99	47	5	—	498	16	83	181	143	61	12	2
One degree of enlargement	30	—	4	10	10	6	—	—	20	—	2	11	7	—	—	—
Two degrees of enlargement	31	1	—	11	8	11	—	—	32	1	4	14	8	4	1	—
Three degrees of enlargement	12	—	—	—	6	5	—	1	17	—	4	4	6	3	—	—
Four degrees of enlargement	6	—	—	—	5	1	—	—	8	—	1	2	4	—	1	—
Degree of enlargement unknown	3	—	—	2	1	—	—	—	4	—	—	1	2	1	—	—
No report on enlargement	10	—	—	6	4	—	—	—	10	—	—	5	2	3	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2
Peripheral Edema																
No edema	390	7	68	140	114	56	4	1	525	16	88	203	147	60	9	2
One degree of edema	20	1	3	7	4	5	—	—	28	—	2	7	13	4	2	—
Two degrees of edema	17	1	1	3	7	4	1	—	15	—	2	5	3	3	2	—
Three degrees of edema	6	—	—	—	4	2	—	—	7	1	1	1	2	2	—	—
Four degrees of edema	2	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—
Degree of edema unknown	2	—	—	—	1	1	—	—	6	—	1	—	4	—	1	—
No report on edema	5	—	—	1	2	2	—	—	8	—	—	2	3	3	—	—
Total cases	442	9	72	152	133	70	5	1	589	17	94	218	172	72	14	2

* For percentage of cases with a known record in the total sample in combined categories, see Tables 48, 52, and 56, of the text. Percentages for selected components also appear in Tables 46, 47, 50, 51, 54, and 55 of the text.

APPENDIX TABLE 14

DEGREE OF PULMONARY EDEMA, LIVER ENLARGEMENT, AND PERIPHERAL EDEMA, BY PERIOD OF ILLNESS: Number of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Pulmonary Edema, Liver Enlargement, and Peripheral Edema of Various Degrees during the First Week and from the Second through the Sixth Week of Observation

Maximum Degree of Condition Reported[a]	Number of Cases[b]					
	1st Week			2nd through 6th Week		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
Pulmonary Edema						
No edema	779	322	466	816	346	470
One degree of edema	76	38	38	36	17	19
Two degrees of edema	87	44	43	31	16	15
Three degrees of edema	39	18	21	16	6	10
Four degrees of edema	24	10	14	7	4	3
Degree unknown	11	4	7	32	15	17
Total with symptoms	237	114	123	122	58	64
No report on symptoms	15	6	9	21	6	15
Total cases at beginning of the period	1031	442	589	959	410	549

Maximum Degree of Condition Reported[a]	Total Sample (1st Week)	Control Group (1st Week)	Treated Group (1st Week)	Total Sample (2nd–6th Week)	Control Group (2nd–6th Week)	Treated Group (2nd–6th Week)
Liver Enlargement						
No enlargement	871	361	938	823	342	456
One degree of enlargement	44	25	19	27	15	12
Two degrees of enlargement	53	25	23	23	14	13
Three degrees of enlargement	22	9	13	17	6	11
Four degrees of enlargement	9	4	5	7	2	5
Degree unknown	7	4	3	11	7	4
Total with symptoms	135	67	68	91	44	47
No report on symptoms	25	14	11	40	24	16
Total cases at beginning of the period	1031	442	589	959	410	549

Maximum Degree of Condition Reported[a]	Total Sample (1st Week)	Control Group (1st Week)	Treated Group (1st Week)	Total Sample (2nd–6th Week)	Control Group (2nd–6th Week)	Treated Group (2nd–6th Week)
Peripheral Edema						
No edema	936	401	535	892	381	511
One degree of edema	36	16	20	19	8	11
Two degrees of edema	26	12	14	7	6	1
Three degrees of edema	10	4	6	4	2	2
Four degrees of edema	1	1	—	1	1	—
Degree unknown	9	4	5	17	7	10
Total with symptoms	82	37	45	48	24	24
No report on symptoms	13	4	9	19	5	14
Total cases at beginning of the period	1031	442	589	959	410	549

[a] Symptoms from the second through the sixth week were probably underreported to a greater extent than indicated.

[b] For percentages based on these numbers, see Tables 49, 53, and 57 of the text.

APPENDIX TABLE 15

ARRHYTHMIAS, ANY TYPE: Number of Cases in the Total Sample and in the Control and Treated Groups for Whom Any Type of Abnormal Rhythm Was Reported for the First Week and from the Second through the Sixth Week of Observation

Period of Illness and Treatment Group	Number of Cases with Any Arrhythmia[a]							
	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown
First week:								
Total sample	366	11	45	124	100	70	14	2
Control group	162	5	24	48	46	35	3	1
Treated group	204	6	21	76	54	35	11	1
Second through sixth week:								
Total sample	242	7	33	76	72	45	7	2
Control group	112	3	14	37	30	25	2	1
Treated group	130	4	19	39	42	20	5	1

[a] For abnormalities included, see footnote b, Table 58 of the text. For the number of cases with a report on heart rhythms and percentage of cases with any arrhythmias, see the same Table.

APPENDIX TABLE 16

SPECIFIC ARRHYTHMIAS: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups for Whom Specific Types of Arrhythmias and Conduction Defects Were Reported for the First Week and from the Second through the Sixth Week of Observation

Type of Arrhythmia[a]	Cases with Specific Arrhythmias											
	Number of Cases						Percentage of Cases[b]					
	1st Week			2nd through 6th Week			1st Week			2nd through 6th Week		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
Auricular fibrillation	69	30	39	48	24	24	6.8	6.9	6.7	5.2	6.1	4.5
Auricular flutter	10	2	8	11	5	6	1.0	.5	1.4	1.2	1.3	1.1
Ventricular fibrillation	6	2	4	3	2	1	.6	.5	.7	.3	.5	.2
Heart block												
A-V block												
Delayed conduction	12	6	6	4	3	1	1.2	1.4	1.0	.4	.8	.2
Incomplete block	18	12	6	4	2	2	1.8	2.8	1.0	.4	.5	.4
Complete block	15	9	6	3	1	2	1.5	2.1	1.0	.3	.3	.4
A-V dissociation	3	—	3	4	1	3	.3	0.0	.5	.4	.3	.6
Type indeterminate	—	—	—	1	1	—	0.0	0.0	0.0	.1	.3	0.0
Bundle branch block:												
Left or right	67	20	47	37	11	26	6.6	4.6	8.1	4.0	2.8	4.9
Delayed ventricular conduction	13	3	10	9	3	6	1.3	.7	1.7	1.0	.8	1.1
Dropped beats	3	3	—	—	—	—	.3	7	0.0	0.0	0.0	0.0
Paroxysmal tachycardia	8	2	6	9	1	8	.8	.5	1.0	1.0	.3	1.5
Premature contractions	78	34	44	55	25	30	7.7	7.9	7.6	6.0	6.4	5.7
Ectopic beats or extrasystoles not specified as premature	71	32	39	51	21	30	7.0	7.4	6.7	5.5	5.4	5.7
Gallop rhythm	63	29	34	32	14	18	6.2	6.7	5.8	3.5	3.6	3.4
Syndromes												
Adams-Stokes	4	1	3	1	—	1	.4	.2	5	.1	0.0	.2
Pulsus alternus	1	1	—	—	—	—	.1	.2	0.0	0.0	0.0	0.0
Pulsus bigeminy	10	4	6	7	2	5	1.0	.9	1.0	8	.5	.9
Pulsus trigeminy	1	—	1	2	1	1	.1	0.0	.2	2	.3	.2
Miscellaneous types[c]	7	3	4	5	1	4	.7	.7	.7	.5	.3	.8
Type indeterminate	7	1	6	7	3	4	.7	2	1.0	.8	.8	.8
Total cases with report on arrhythmia	1015	433	582	921	392	529	100.0	100.0	100.0	100.0	100.0	100.0
Total cases at beginning of period	1031	442	589	959	410	549	—	—	—	—	—	—

[a] Counts for persistent tachycardia and bradycardia, and sinus arrhythmia are not included since these types of rhythms were considered grossly underreported

[b] Based on numb…

[c] In the tot…

case in later w…

pacemaker, for…

and auriculov…

…case in the later weeks and none in the first week

APPENDIX TABLE 17

MAXIMUM PULSE, FIRST WEEK: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Having Maximum Pulse Rates at Various Levels during the First Week of the Illness, by Survival Status for the Six-Week Period

Maximum Pulse Rate[a]	Number of Cases									Percentage of Cases[b]								
	Total Sample			Control Group			Treated Group			Total Sample			Control Group			Treated Group		
	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period
Under 60	3	3	—	1	1	—	2	2	—	.3	1.7	—	.3	1.1	—	.4	2.2	—
60-69	8	1	7	3	1	2	5	—	5	.8	.6	.9	.7	1.1	.7	.9	—	1.1
70-79	26	2	24	12	—	12	14	2	12	2.7	1.1	3.1	3.0	—	3.8	2.6	2.2	2.6
80-89	151	9	142	67	4	63	84	5	79	15.9	5.0	18.4	16.6	4.6	20.0	15.3	5.6	17.2
90-99	171	16	155	69	6	63	102	10	92	18.0	9.0	20.0	17.1	6.8	20.0	18.6	11.1	20.1
Total under 100	359	31	328	152	12	140	207	19	188	37.7	17.4	42.4	37.7	13.6	44.5	37.8	21.1	41.0
100-109	224	38	186	81	17	64	143	21	122	23.6	21.3	24.1	20.1	19.3	20.4	26.1	23.3	26.6
110-119	103	21	82	58	12	46	45	9	36	10.8	11.8	10.6	14.4	13.7	14.6	8.2	10.0	7.9
120-129	168	49	120	74	28	46	94	20	74	17.7	27.0	15.5	18.3	31.8	14.6	17.2	22.2	16.2
130-139	52	15	34	20	9	11	32	9	23	5.5	10.1	4.4	5.0	10.2	3.6	5.8	10.0	5.0
140-149	20	8	12	9	4	5	11	4	7	2.1	4.5	1.6	2.2	4.6	1.6	2.0	4.5	1.5
150-159	7	3	4	1	1	—	6	2	4	.7	1.7	.5	.3	1.1	—	1.1	2.2	.9
160-169	10	6	4	4	3	1	6	3	3	1.1	3.4	.5	1.0	3.4	.3	1.1	3.3	.7
170 and over	8	5	3	4	2	2	4	3	1	.8	2.8	.4	1.0	2.3	.6	.7	3.3	.2
Total 100 and over	592	147	445	251	76	175	341	71	270	62.3	82.6	57.6	62.3	86.4	55.5	62.2	78.9	59.0
Total cases with report on pulse rate	951	178	773	403	88	315	548	90	458	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total cases	1031	190	841	442	96	346	589	94	495	—	—	—	—	—	—	—	—	—

[a] Cases varied greatly in the number of reported rates on which maximums could be based.

[b] Based on number of cases with a report on pulse rate

... through the Sixth Week of the Illness, by Survival Status for the Second through the Sixth Week

Maximum Pulse Rate[a]	Number of Cases: Total Sample: All Cases Surviving to Beginning of Second Week	Number of Cases: Total Sample: Cases Dying from the Second through the Sixth Week	Number of Cases: Total Sample: Cases Surviving Six-Week Period	Number of Cases: Control Group: All Cases Surviving to Beginning of Second Week	Number of Cases: Control Group: Cases Dying from the Second through the Sixth Week	Number of Cases: Control Group: Cases Surviving Six-Week Period	Number of Cases: Treated Group: All Cases Surviving to Beginning of Second Week	Number of Cases: Treated Group: Cases Dying from the Second through the Sixth Week	Number of Cases: Treated Group: Cases Surviving Six-Week Period	Percentage of Cases[b]: Total Sample: All Cases Surviving to Beginning of Second Week	Percentage of Cases[b]: Total Sample: Cases Dying from the Second through the Sixth Week	Percentage of Cases[b]: Total Sample: Cases Surviving Six-Week Period	Percentage of Cases[b]: Control Group: All Cases Surviving to Beginning of Second Week	Percentage of Cases[b]: Control Group: Cases Dying from the Second through the Sixth Week	Percentage of Cases[b]: Control Group: Cases Surviving Six-Week Period	Percentage of Cases[b]: Treated Group: All Cases Surviving to Beginning of Second Week	Percentage of Cases[b]: Treated Group: Cases Dying from the Second through the Sixth Week	Percentage of Cases[b]: Treated Group: Cases Surviving Six-Week Period
Under 60	3	1	2	2	—	2	1	1	—	3	.9	2	.5	—	6	.2	1.9	—
60–69	4	—	4	2	—	2	2	—	2	4	—	5	.5	—	.6	.4	—	.4
70–79	15	2	13	6	—	6	9	2	7	1.6	1.8	1.6	1.5	—	1.7	1.8	3.8	1.4
80–89	201	7	194	94	2	92	107	5	102	21.2	6.2	23.2	23.2	3.3	20.7	19.7	9.6	20.8
90–99	264	16	218	97	6	91	167	10	157	27.8	14.1	29.6	23.0	9.8	26.5	30.7	19.3	31.9
Total under 100	457	26	461	201	8	193	286	18	268	51.3	23.0	55.1	49.6	13.1	50.1	52.6	31.6	51.5
100–109	250	23	227	96	13	84	154	11	143	26.3	20.4	27.1	23.7	10.7	21.4	28.3	21.2	29.1
110–119	86	20	66	39	11	28	47	9	38	9.1	17.7	7.9	9.7	18.0	8.1	8.0	17.4	7.7
120–129	78	21	57	45	17	28	33	4	29	8.2	18.6	6.8	11.1	27.9	8.1	6.1	7.7	5.9
130–139	24	9	15	14	7	7	10	2	8	2.5	8.0	1.8	3.5	11.5	2.1	1.8	3.8	1.0
140–149	8	5	3	4	3	1	4	2	2	8	4.1	4	1.0	4.9	.3	.7	3.8	.4
150–159	7	4	3	1	1	—	6	3	3	8	3.5	4	.2	1.6	—	1.1	5.8	.6
160–169	2	1	1	1	—	1	1	1	—	2	.9	.1	.2	—	.3	.2	1.9	—
170 and over	7	4	3	4	2	2	3	2	1	.8	3.5	4	1.0	3.3	.6	.6	3.8	2
Total 100 and over	462	87	375	201	53	151	258	34	221	18.7	77.0	44.9	50.4	86.9	43.9	47.4	65.4	45.5
Total cases with report on pulse rate	949	113	836	405	61	344	544	52	492	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total cases at beginning of period	959	118	841	410	61	346	519	54	495	—	—	—	—	—	—	—	—	—

[a] Cases varied greatly in the number of reported rates on which maximums could be based

[b] Based on number of cases with a report on pulse rate

APPENDIX TABLE 17

MAXIMUM PULSE, FIRST WEEK: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Having Maximum Pulse Rates at Various Levels during the First Week of the Illness, by Survival Status for the Six-Week Period

Maximum Pulse Rate[a]	Number of Cases: Total Sample: All Cases	Total Sample: Cases Dying within Six Weeks	Total Sample: Cases Surviving Six-Week Period	Control Group: All Cases	Control Group: Cases Dying within Six Weeks	Control Group: Cases Surviving Six-Week Period	Treated Group: All Cases	Treated Group: Cases Dying within Six Weeks	Treated Group: Cases Surviving Six-Week Period	Percentage of Cases[b]: Total Sample: All Cases	Total Sample: Cases Dying within Six Weeks	Total Sample: Cases Surviving Six-Week Period	Control Group: All Cases	Control Group: Cases Dying within Six Weeks	Control Group: Cases Surviving Six-Week Period	Treated Group: All Cases	Treated Group: Cases Dying within Six Weeks	Treated Group: Cases Surviving Six-Week Period
Under 60	3	3	—	1	1	—	2	2	—	.3	1.7	—	.3	1.1	—	.4	2.2	—
60-69	8	1	7	3	1	2	5	—	5	.8	.6	.9	.7	1.1	.7	.9	—	1.1
70-79	26	2	24	12	—	12	14	2	12	2.7	1.1	3.1	3.0	—	3.8	2.6	2.2	2.6
80-89	151	9	142	67	4	63	84	5	79	15.9	5.0	18.4	16.6	4.6	20.0	15.3	5.6	17.2
90-99	171	16	155	69	6	63	102	10	92	18.0	9.0	20.0	17.1	6.8	20.0	18.6	11.1	20.1
Total under 100	359	31	328	152	12	140	207	19	188	37.7	17.4	42.4	37.7	13.6	44.5	37.8	21.1	41.0
100-109	224	38	186	81	17	64	143	21	122	23.6	21.3	24.1	20.1	19.3	20.4	26.1	23.4	26.6
110-119	103	21	82	58	12	46	45	9	36	10.8	11.8	10.6	14.4	13.7	14.6	8.2	10.0	7.9
120-129	168	48	120	74	28	46	94	20	74	17.7	27.0	15.5	18.3	31.8	14.6	17.2	22.2	16.2
130-139	52	18	34	20	9	11	32	9	23	5.5	10.1	4.4	5.0	10.2	3.5	5.8	10.0	5.0
140-149	20	8	12	9	4	5	11	4	7	2.1	4.5	1.6	2.2	4.5	1.6	2.0	4.4	1.5
150-159	7	3	4	1	1	—	6	2	4	.7	1.7	.5	.2	1.1	—	1.1	2.2	.9
160-169	10	6	4	4	3	1	6	3	3	1.1	3.4	.5	1.0	3.4	.3	1.1	3.3	.7
170 and over	8	5	3	4	2	2	4	3	1	.8	2.8	.4	1.0	2.3	.6	.7	3.3	.2
Total 100 and over	592	147	445	251	76	175	341	71	270	62.3	82.6	57.6	62.3	86.4	55.5	62.2	78.9	59.0
Total cases with report on pulse rate	951	178	773	403	88	315	548	90	458	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total cases	1031	190	841	442	96	346	589	94	495	—	—	—	—	—	—	—	—	—

[a] Cases varied greatly in the number of reported rates on which maximums could be based.

[b] Based on number of cases with a report on pulse rate

APPENDIX TABLE 20

MAXIMUM TEMPERATURE, SECOND THROUGH SIXTH WEEK: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Having Maximum Rectal Temperatures at Various Levels from the Second through the Sixth Week of the Illness, by Survival Status for the Second through the Sixth Week

Maximum Rectal Temperature (Fahrenheit)[a]	Number of Cases									Percentage of Cases[b]								
	Total Sample			Control Group			Treated Group			Total Sample			Control Group			Treated Group		
	All Cases Surviving to Beginning of Second Week	Cases Dying from the Second through the Sixth Week	Cases Surviving Six-Week Period	All Cases Surviving to Beginning of Second Week	Cases Dying from the Second through the Sixth Week	Cases Surviving Six-Week Period	All Cases Surviving to Beginning of Second Week	Cases Dying from the Second through the Sixth Week	Cases Surviving Six-Week Period	All Cases Surviving to Beginning of Second Week	Cases Dying from the Second through the Sixth Week	Cases Surviving Six-Week Period	All Cases Surviving to Beginning of Second Week	Cases Dying from the Second through the Sixth Week	Cases Surviving Six-Week Period	All Cases Surviving to Beginning of Second Week	Cases Dying from the Second through the Sixth Week	Cases Surviving Six-Week Period
Afebrile (below 100.0°)	174	13	161	81	7	74	93	6	87	18.5	11.6	19.4	20.1	11.7	21.6	17.2	11.5	17.8
100.0°–100.9°	395	22	373	149	8	141	246	14	232	41.9	19.6	44.0	37.0	13.3	41.1	45.6	26.9	47.6
101.0°–101.9°	191	22	169	80	10	70	111	12	99	20.3	19.6	20.3	19.9	16.7	20.4	20.6	23.1	20.3
102.0°–102.9°	98	18	80	47	10	37	51	8	43	10.4	16.1	9.6	11.7	16.7	10.8	9.4	15.4	8.8
103.0°–103.9°	48	17	31	23	11	12	25	6	19	5.1	15.2	3.7	5.7	18.3	3.5	4.6	11.6	3.9
104.0°–104.9°	22	9	13	17	9	8	5	—	5	2.3	8.0	1.6	4.2	15.0	2.3	.9	—	1.0
105.0°–105.9°	7	4	3	3	3	—	4	1	3	.7	3.6	.4	.7	5.0	—	.7	1.9	.6
106.0°–106.9°	6	5	1	3	2	1	3	3	—	.6	4.5	.1	.7	3.3	.3	.6	5.8	—
107.0°–107.9°	1	1	—	—	—	—	1	1	—	.1	.9	—	—	—	—	.2	1.9	—
108.0°–108.9°	1	1	—	—	—	—	1	1	—	.1	.9	—	—	—	—	.2	1.9	—
Total cases with report on temperature	943	112	831	403	60	343	540	52	488	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total cases at beginning of period	959	118	841	410	64	346	549	54	495	—	—	—	—	—	—	—	—	—

[a] Maximums are in some cases understated since for 19 cases in the total sample only one or two temperature readings were reported for the second through the sixth week. When the reported temperatures were taken by mouth, one degree was added to approximate the rectal equivalent. Centrigrade readings were converted to their Fahrenheit equivalent.

[b] Based on number of cases with a report on temperature.

APPENDIX TABLE 19

MAXIMUM TEMPERATURE, FIRST WEEK: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Having Maximum Rectal Temperatures at Various Levels during the First Week of the Illness, by Survival Status for the Six-Week Period

Maximum Rectal Temperature (Fahrenheit)[a]	Number of Cases									Percentage of Cases[b]								
	Total Sample			Control Group			Treated Group			Total Sample			Control Group			Treated Group		
	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period
Afebrile (below 100.0°)	83	5	80	33	3	30	52	2	50	9.0	2.8	10.4	8.1	3.3	9.5	9.6	2.2	11.1
100.0°–100.9°	209	21	155	89	6	83	120	15	105	22.1	11.7	21.5	21.9	6.7	26.3	22.1	16.7	23.2
101.0°–101.9°	261	47	214	105	24	81	156	23	133	27.5	26.1	27.9	25.9	26.7	25.6	28.8	25.6	29.4
102.0°–102.9°	242	42	200	100	21	79	142	21	121	25.6	23.3	26.0	24.6	23.3	25.0	26.2	23.3	26.8
103.0°–103.9°	110	44	66	57	25	32	53	19	34	11.6	24.4	8.6	14.1	27.8	10.1	9.8	21.1	7.5
104.0°–104.9°	32	14	18	16	7	9	16	7	9	3.4	7.8	2.3	3.9	7.8	2.9	2.9	7.8	2.0
105.0°–105.9°	4	2	2	3	1	2	1	1	—	.4	1.1	.3	.7	1.1	.6	.2	1.1	—
106.0°–106.9°	2	2	—	2	2	—	—	—	—	.2	1.1	—	.5	2.2	—	—	—	—
107.0°–107.9°	3	3	—	1	1	—	2	2	—	.3	1.7	—	.3	1.1	—	.4	2.2	—
Total cases with report on temperature	945	180	765	406	90	316	542	90	452	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total cases	1031	190	841	412	96	316	589	94	493	—	—	—	—	—	—	—	—	—

[a] Maximums are in some cases understated since for 59 cases in the total sample only 1 or 2 temperature readings were reported for the first week. When the reported temperatures were taken by mouth, 1 degree was added to approximate the rectal equivalent. Centigrade readings were converted to their Fahrenheit equivalent.

[b] Based on number of cases with a report on temperature.

APPENDIX TABLE 21 (cont.)

Difference (in mms.) between Average Reported Blood Pressure on Lowest Hospital Day and Usual Level prior to the Illness[a]	Number of Cases: Total Sample: All Cases	Total Sample: Cases Dying within Six Weeks	Total Sample: Cases Surviving Six-Week Period	Control Group: All Cases	Control Group: Cases Dying within Six Weeks	Control Group: Cases Surviving Six-Week Period	Treated Group: All Cases	Treated Group: Cases Dying within Six Weeks	Treated Group: Cases Surviving Six-Week Period	Percentage of Cases[b]: Total Sample: All Cases	Total Sample: Cases Dying within Six Weeks	Total Sample: Case Surviving Six-Week Period	Control Group: All Cases	Control Group: Cases Dying within Six Weeks	Control Group: Cases Surviving Six-Week Period	Treated Group: All Cases	Treated Group: Cases Dying within Six Weeks	Treated Group: Cases Surviving Six-Week Period
Diastolic Blood Pressure																		
No drop, higher than usual level by—																		
40-49	1	—	1	—	—	—	1	—	1	.3	—	.3	—	—	—	.5	—	.6
30-39	1	—	1	1	—	1	—	—	—	.3	—	.3	.6	—	.8	—	—	—
20-29	2	1	1	1	1	—	1	—	1	.5	1.3	.3	.6	2.8	—	.5	—	.6
10-19	7	1	6	3	1	2	4	—	4	1.9	1.3	2.0	2.0	2.8	1.7	1.8	—	2.2
1-9	14	—	14	6	—	8	6	—	6	3.7	—	4.7	5.2	—	6.8	2.7	—	3.3
Total cases higher	25	2	23	13	2	11	12	—	12	6.7	2.6	7.6	8.4	5.6	9.3	5.5	—	6.6
Same as usual level	20	4	16	10	2	8	10	2	8	5.3	5.4	5.4	6.5	5.6	6.8	4.5	5.1	4.4
Below usual level by—																		
5-9	39	8	33	9	3	6	30	3	27	10.4	8.0	11.0	5.8	8.3	5.1	13.6	7.7	14.8
10-19	78	11	67	32	5	27	46	6	40	20.8	14.6	22.3	20.8	13.9	22.9	20.8	15.4	22.0
20-29	92	17	75	36	10	26	56	7	49	24.5	22.7	25.0	23.4	27.8	22.0	25.3	17.9	25.9
30-39	63	14	49	30	5	25	33	9	24	18.8	18.7	16.3	19.5	13.9	21.2	14.9	23.1	13.2
40-49	29	7	22	13	3	10	16	4	12	7.7	9.3	7.4	8.5	8.3	8.5	7.2	10.3	6.6
50-59	12	5	7	5	3	2	7	2	5	3.2	6.7	2.4	3.3	8.3	1.7	3.2	5.1	2.7
60-69	12	8	6	4	2	2	8	4	4	3.2	8.0	2.0	2.6	5.5	1.7	3.6	10.3	2.2
70-79	4	3	1	1	1	—	3	2	1	1.1	4.0	.3	.6	2.8	—	1.4	5.1	.5
80 and over	1	—	1	1	—	1	—	—	—	.3	—	.3	.6	—	.8	—	—	—
Total cases lower	330	69	261	131	32	99	199	37	162	88.0	92.0	87.0	85.1	88.8	83.9	90.0	94.9	87.0
Total cases with known difference	375	75	300	154	36	118	221	39	182	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total cases	1031	190	841	442	95	346	589	94	495	—	—	—	—	—	—	—	—	—

[a] Understatements of the differences are doubtless frequent both because patients were sometimes hospitalized *after* the acute attack had passed and because hospital readings may *not* have been taken at the lowest points In addition, for a few patients, differences had to be based on one or two hospital readings during the first week, since hospitalization was delayed

[b] Based on number of cases with known differences

APPENDIX TABLE 21

MAXIMUM DROPS IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, FIRST WEEK: Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing *Maximum Drops of Various Amounts in Systolic and Diastolic Blood Pressure during the First Week of the Illness among Those for Whom a Blood Pressure Level prior to the Present Illness Was Reported, by Survival Status for the Six-Week Period*

Difference (in mms.) between Average Reported Blood Pressure on Lowest Hospital Day and Usual Level prior to the Illness[a]	Number of Cases									Percentage of Cases[b]								
	Total Sample			Control Group			Treated Group			Total Sample			Control Group			Treated Group		
	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period	All Cases	Cases Dying within Six Weeks	Cases Surviving Six-Week Period
Systolic Blood Pressure																		
No drop; higher than usual level by—																		
30-39	3	1	2	1	1	—	2	—	2	.6	1.1	.5	.5	2.3	—	.7	—	.8
20-29	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10-19	9	1	8	3	1	2	6	—	6	1.9	1.1	2.1	1.6	2.3	1.4	2.1	—	2.6
1-9	5	—	5	3	—	3	2	—	2	1.1	—	1.3	1.6	—	2.0	.7	—	.8
Total cases higher	17	2	15	7	2	5	10	—	10	3.6	2.2	3.9	3.7	4.6	3.4	3.5	—	4.2
Same as usual level	14	—	14	6	—	6	8	—	8	2.9	—	3.6	3.2	—	4.1	2.8	—	3.4
Below usual level by—																		
1-9	15	1	14	6	1	5	9	—	9	3.1	1.0	3.6	3.2	2.3	3.4	3.1	—	3.3
10-19	52	8	44	26	3	23	26	5	21	10.9	8.6	11.5	13.6	6.9	15.7	9.1	10.0	8.9
20-29	59	10	49	17	6	11	42	4	38	12.4	10.8	12.6	8.9	14.0	7.3	11.6	8.0	16.0
30-39	47	3	44	17	1	16	30	2	28	9.8	3.2	11.3	8.9	2.3	10.9	10.4	4.0	11.5
40-49	61	8	53	20	2	18	41	6	35	12.8	8.6	13.8	10.5	4.7	13.2	14.3	12.0	14.5
50-59	57	10	47	31	5	26	26	5	21	11.9	10.8	12.2	16.3	11.6	17.7	9.1	10.0	5.9
60-69	35	11	24	14	6	8	21	5	16	7.3	11.8	6.3	7.4	14.0	5.4	7.3	10.0	6.8
70-79	40	12	28	14	5	9	26	7	19	8.4	12.9	7.3	7.4	11.6	6.1	9.1	14.0	8.0
80-89	19	3	16	7	3	5	12	1	11	4.0	3.2	4.2	3.7	4.7	3.4	4.2	2.0	4.6
90-99	29	10	19	12	2	10	17	8	9	6.1	10.8	4.9	6.3	4.7	6.8	5.9	16.0	3.8
100-109	16	7	9	7	4	3	9	3	6	3.4	7.5	2.3	3.7	9.3	2.0	3.1	6.0	2.5
110 and over	16	8	8	6	4	2	10	4	6	3.4	8.6	2.1	3.2	9.3	1.4	3.5	8.0	2.5
Total cases lower	446	91	355	177	41	136	269	50	219	93.5	97.8	92.5	93.1	95.4	92.5	93.7	100.0	97.4
Total cases with known difference	477	93	384	190	43	147	287	50	237	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total cases	1031	190	841	442	96	346	589	94	495	—	—	—	—	—	—	—	—	—

Total cases with known difference	463	51	402	188	28	100	205	23	212	100.0	100.0	100.0	100.0	*100.0*	100.0	100.0	*100.0*	100.0
Total cases at beginning of period	050	118	841	410	64	346	549	51	495	—	—	—	—	—	—	—	—	—
Diastolic Blood Pressure																		
No drop; higher than usual level by—																		
20–29	2	2	—	2	2	—	—	—	—	.6	4.3	—	1.3	*8.0*	—	—	—	—
10–19	6	1	5	2	—	2	4	1	3	1.7	2.2	1.6	1.3	—	1.5	1.9	*4.7*	1.6
1–9	7	4	3	3	3	—	4	1	3	1.9	8.7	.9	1.9	*12.0*	—	1.9	*4.8*	1.6
Total cases higher	15	7	8	7	5	2	8	2	6	4.2	15.2	2.5	4.5	*20.0*	1.5	3.8	*9.5*	3.2
Same as usual level	11	—	11	5	—	5	6	—	6	3.0	—	3.5	3.3	—	3.9	2.9	—	3.2
Below usual level by—																		
1–9	23	2	21	11	2	9	12	—	12	6.3	4.3	6.6	7.2	*8.0*	7.0	5.8	—	6.4
10–19	70	6	64	27	2	25	43	4	39	19.3	13.1	20.3	17.5	*8.0*	19.4	20.7	*19.0*	20.9
20–29	97	7	90	43	4	39	54	3	51	26.8	15.2	28.5	27.9	*16.0*	30.2	25.9	*14.3*	27.3
30–39	77	9	68	29	5	24	48	4	44	21.3	19.6	21.5	18.8	*20.0*	18.6	23.1	*19.0*	23.5
40–49	35	7	28	18	4	14	17	3	14	9.6	15.2	8.9	11.7	*16.0*	10.9	8.2	*14.3*	7.5
50–59	18	3	15	9	—	9	9	3	6	5.0	6.6	4.7	5.9	—	7.0	4.3	*14.3*	3.2
60–69	9	2	7	3	1	2	6	1	5	2.5	4.3	2.2	1.9	*4.0*	1.5	2.9	*4.8*	2.7
70–79	5	1	4	—	—	—	5	1	4	1.4	2.2	1.3	—	—	—	2.4	*4.8*	2.1
80 and over	2	2	—	2	2	—	—	—	—	.6	4.3	—	1.3	*8.0*	—	—	—	—
Total cases lower	336	39	297	142	20	122	194	19	175	92.8	84.8	94.0	92.2	*80.0*	91.6	93.3	*90.5*	93.6
Total cases with known difference	362	46	316	154	25	129	208	21	187	100.0	100.0	100.0	100.0	*100.0*	100.0	100.0	*100.0*	100.0
Total cases at beginning of period...	959	118	841	410	64	346	549	51	495	—	—	—	—	—	—	—	—	—

Note: *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] See footnote a, Appendix Table 21. [b] Based on number of cases with known differences.

MAXIMUM DROPS IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, SECOND THROUGH SIXTH WEEK: *Number and Percentage of Cases in the Total Sample and in the Control and Treated Groups Showing Maximum Drops of Various Amounts in Systolic and Diastolic Blood Pressure during the Second through the Sixth Week of the Illness among Those for Whom a Blood Pressure Level prior to the Present Illness Was Reported, by Survival Status for the Second through the Sixth Week*

Difference (in mms.) between Average Reported Blood Pressure on Lowest Hospital Day and Usual Level prior to the Illness[a]	Number of Cases: Total Sample: All Cases Surviving to Beginning of Second Week	Total Sample: Cases Dying from the Second through the Sixth Week	Total Sample: Cases Surviving Six-Week Period	Control Group: All Cases Surviving to Beginning of Second Week	Control Group: Cases Dying from the Second through the Sixth Week	Control Group: Cases Surviving Six-Week Period	Treated Group: All Cases Surviving to Beginning of Second Week	Treated Group: Cases Dying from the Second through the Sixth Week	Treated Group: Cases Surviving Six-Week Period	Percentage of Cases[b]: Total Sample: All Cases Surviving to Beginning of Second Week	Total Sample: Cases Dying from the Second through the Sixth Week	Total Sample: Cases Surviving Six-Week Period	Control Group: All Cases Surviving to Beginning of Second Week	Control Group: Cases Dying from the Second through the Sixth Week	Control Group: Cases Surviving Six-Week Period	Treated Group: All Cases Surviving to Beginning of Second Week	Treated Group: Cases Dying from the Second through the Sixth Week	Treated Group: Cases Surviving Six-Week Period
Systolic Blood Pressure																		
No drop; higher than usual level by—																		
20-29	1	—	1	1	—	1	—	—	—	.2	—	.3	.5	—	.6	—	—	—
10-19	4	1	3	3	1	2	1	—	1	.9	2.0	.7	1.6	*3.6*	1.3	.4	—	.4
1-9	4	—	4	—	—	—	4	—	4	.9	—	1.0	—	—	—	1.5	—	1.7
Total cases higher	9	1	8	4	1	3	5	—	5	2.0	2.0	2.0	2.1	*3.6*	1.9	1.9	—	2.1
Same as usual level	9	1	8	2	1	1	7	—	7	2.0	2.0	2.0	1.1	*3.6*	.6	2.6	—	2.9
Below usual level by—																		
1-9	14	—	14	3	—	3	11	—	11	3.1	—	3.5	1.6	—	1.9	4.1	—	4.5
10-19	26	2	24	17	2	15	9	—	9	5.7	3.9	6.0	9.0	*7.1*	9.4	3.4	—	3.7
20-29	58	6	52	24	4	20	31	2	32	12.8	11.8	12.9	12.8	*14.3*	12.5	12.8	*8.7*	13.2
30-39	63	5	58	22	1	21	41	4	37	13.9	9.8	14.4	11.7	*3.6*	13.1	15.5	*17.4*	15.3
40-49	60	7	53	26	2	21	31	5	29	13.3	13.7	13.2	13.8	*7.1*	15.0	12.8	*21.8*	12.0
50-59	58	6	52	26	6	20	32	—	32	12.8	11.8	12.9	13.8	*21.5*	12.5	12.1	—	13.2
60-69	41	5	36	18	1	17	23	4	19	9.1	9.8	9.0	9.6	*3.6*	10.6	8.7	*17.4*	7.9
70-79	31	4	27	12	3	9	19	1	18	6.8	7.8	6.7	6.4	*10.7*	5.6	7.2	*4.3*	7.4
80-89	34	6	28	15	3	12	19	3	16	7.5	11.8	7.0	8.0	*10.7*	7.5	7.2	*13.1*	6.6
90-99	21	1	20	7	—	7	14	1	13	4.6	2.0	5.0	3.7	—	4.4	5.3	*4.3*	5.4
100-109	16	3	13	8	2	6	8	1	7	3.5	5.8	3.2	4.3	*7.1*	3.7	3.0	*4.3*	2.9
110 and over	13	4	9	4	2	2	9	2	7	2.9	7.8	2.2	2.1	*7.1*	1.3	3.4	*8.7*	2.9
Total cases lower	435	49	386	182	26	156	253	23	230	96.0	96.0	96.0	96.8	[illegible]	97.5	95.6	*100.0*	95.0

All cases:																					
Under 10	*26*	*9*	*17*	*2*	*1*	*1*	*9*	*5*	*4*	*1*	*1*	—	*7.7*	—[d]	*5.0*	*34 6*	—[d]	*23 5*	*5 8*	—[d]	*0 0*
40–49	*166*	*72*	*94*	*23*	*11*	*12*	*38*	*16*	*22*	*10*	*3*	7	13 8	15 3	12 8	22 0	22.2	23 4	6 0	4 2	7 5
50–59	*370*	*152*	*218*	*70*	*29*	*41*	*63*	*24*	*39*	*19*	*11*	8	18 0	10.1	18 8	17.0	15 8	17 9	5.1	7.2	3 7
60–69	*305*	*133*	*172*	*67*	*33*	*31*	*62*	*28*	*34*	*21*	*9*	12	22 0	24 8	19 8	20 3	21 1	19.8	6 9	0 8	7.0
70–79	*142*	*70*	*72*	*50*	*30*	*20*	*27*	*9*	*18*	*12*	*4*	8	35.2	42 0	27 8	19.0	12 8	25 0	8.5	5.7	11 1
80–89	19	5	14	6	2	4	5	2	3	4	2	2	*31.6*	—[d]	*23 6*	*26 3*	—[d]	*21.4*	*21.1*	—[d]	*14 3*
Age unknown	3	1	2	1	1	—	1	1	—	1	1	—	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]
Total, all cases	1031	442	589	219	107	112	205	85	120	68	31	37	21.2	24.2	19 0	19 0	10.2	20.4	6.6	7 0	6.3

Note· *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such rates particularly unstable.*

[a] For definition of cases included, see footnote a, Table 64 of the text

[b] To compute number or percentage of cases with either initial heart failure or shock, add heart failure and shock columns and subtract the "both" column from total thus computed

[c] Based on total cases in each age and severity subgroup

[d] Not computed since there were less than 10 cases in the sample.

APPENDIX TABLE 23

INITIAL CONGESTIVE HEART FAILURE AND INITIAL SHOCK IN RELATION TO SEVERITY OF ILLNESS AT ONSET, BY AGE: Number and Percentage of Cases Developing Initial Congestive Heart Failure, Initial Shock, or Both among Patients in the Total Sample and in the Control and Treated Groups Whose Illness Was Mild or Moderate at Onset and among Patients Whose Illness Was Severe at Onset, by Age

Age and Severity of Illness at Onset	Total Number of Cases			Number of Cases[a, b] Developing during the First Two Days of Their Illness—									Percentage of Cases[b, c] Developing during the First Two Days of Their Illness—								
				Heart Failure (with or without Shock)			*Shock (with or without Heart Failure)*			*Both Heart Failure and Shock*			*Heart Failure (with or without Shock)*			*Shock (with or without Heart Failure)*			Both Heart Failure and Shock		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
Illness mild or moderate at onset:																					
Under 40	16	4	12	1	1	—	2	1	1	1	1	—	*8.3*	—[d]	*0.0*	*12.5*	—[d]	*8.3*	*8.3*	—[d]	*0.0*
40–49	125	57	68	12	7	5	20	9	11	2	1	1	9.6	12.3	7.4	16.0	15.8	10.2	1.6	1.8	1.5
50–59	263	109	154	37	14	23	33	11	22	6	4	2	14.1	12.9	14.9	12.5	10.1	11.3	2.3	3.7	1.3
60–69	217	101	116	40	22	18	39	21	18	10	4	6	18.4	21.8	15.5	18.0	20.8	15.5	1.6	1.0	5.2
70–79	101	51	50	26	18	8	15	5	10	3	—	3	25.7	35.3	10.0	14.9	9.8	20.0	3.0	*0.0*	*0.0*
80–89	9	3	6	2	1	1	1	1	—	1	1	—	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]
Age unknown	3	1	2	1	1	—	1	1	—	1	1	—	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]
Total mild or moderate	734	326	408	119	64	55	111	49	62	24	12	12	16.2	19.6	13.5	15.1	15.0	15.2	3.3	3.7	2.9
Illness severe at onset:																					
Under 40	10	5	5	1	—	1	7	4	3	—	—	—	*10.0*	—[d]	—[d]	*70.0*	—[d]	—[d]	*0.0*	—[d]	—[d]
40–49	41	15	26	11	4	7	18	7	11	8	2	6	26.8	*26.7*	*20.0*	43.9	*40.0*	*42.3*	10.5	*13.3*	*23.1*
50–59	107	43	64	33	15	18	30	13	17	13	7	6	30.8	34.9	28.1	28.0	30.2	26.6	12.1	16.3	9.4
60–69	88	32	56	27	11	16	23	7	16	11	5	6	30.7	31.4	28.5	26.1	21.8	28.6	12.5	15.0	10.7
70–79	41	19	22	24	12	12	12	4	8	9	4	5	58.5	*63.2*	*54.4*	29.3	*21.1*	*36.4*	22.0	*21.1*	*22.7*
80–89	10	2	8	4	1	3	4	1	3	3	1	2	*40.0*	—[d]	—[d]	*40.0*	—[d]	—[d]	*30.0*	—[d]	—[d]
Total severe	297	116	181	100	43	57	94	36	58	44	19	25	33.7	37.1	31.5	31.6	31.0	32.0	14.8	16.4	13.8

APPENDIX TABLE 25

E AND DEGREE OF CONGESTIVE HEART FAILURE, BY AGE AND TREATMENT ROUPS: Number of Cases Developing Maximum Congestive Heart Failure of Various Degrees and pes during the Six-Week Period of Observation and Percentage of Cases Developing Congestive art Failure of Various Types, by Age and Treatment Groups

pe and Maximum ree of Congestive t Failure[a] Reported at Any Time	Control Group								Treated Group							
	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown	All Ages	Under 40	40-49	50-59	60-69	70-79	80-89	Age Unknown
	Number of Cases															
art failure[b]	234	5	54	100	76	27	2	—	358	16	71	139	109	41	7	2
heart failure only:																
d	20	—	8	9	9	3	1	—	31	—	3	11	8	8	—	—
derate	36	—	4	11	10	10	1	—	34	—	2	19	8	5	—	—
ere	12	1	—	3	4	4	—	—	17	—	2	5	7	4	1	—
gree unknown	—	—	—	—	—	—	—	—	4	—	—	1	2	1	—	—
Total with left heart failure only	78	1	12	23	23	17	2	—	86	—	7	37	25	18	1	—
t heart failure only:																
ld	27	—	3	7	10	6	—	1	25	—	4	17	11	2	1	—
derate	7	1	—	2	2	2	—	—	12	1	2	3	2	3	1	—
vere	3	—	—	1	2	—	—	—	2	—	—	—	2	—	—	—
gree unknown	—	—	—	—	—	—	—	—	1	—	—	—	—	—	1	—
Total with right heart failure only	37	1	2	10	14	8	—	1	50	1	6	20	15	8	3	—
h left and right heart heart failure[c]																
ld	14	1	1	5	4	2	—	—	13	—	—	6	2	4	1	—
oderate	36	1	2	13	12	7	1	—	38	—	6	14	14	2	1	—
vere	13	—	—	1	4	8	—	—	13	—	1	2	7	2	1	—
egree unknown	—	—	—	—	—	—	—	—	1	—	—	—	—	1	—	—
Total with both left and right heart failure	63	2	2	19	23	15	1	—	83	—	7	22	23	10	3	—
Total cases	442	9	72	152	133	70	5	1	569	17	94	218	172	72	14	2
	Percentage of Cases															
heart failure[b]	69.7	—[d]	75.0	65.8	57.1	38.6	—[d]	—[d]	65.9	94.1	73.7	63.8	63.4	56.9	*50.0*	—[d]
t heart failure only	17.6	—[d]	16.6	15.1	17.3	24.3	—[d]	—[d]	24.6	—	7.5	17.0	14.5	22.2	*7.2*	—[d]
ght heart failure only	8.4	—[d]	4.2	6.6	10.5	11.4	—[d]	—[d]	8.8	*5.9*	6.4	9.1	8.7	7.0	*21.4*	—[d]
th left and right heart failure	14.3	—[d]	4.2	12.5	15.1	25.7	—[d]	—[d]	11.0	—	7.4	10.1	13.4	13.9	*21.4*	—[d]
Total cases	100.0	—[d]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

ote *Italics* are used when percen[illegible]
[a] For definition, see footnote a [illegible]
[b] Includes occasional cases for [illegible]
[c] Classified according to the maximum degree of symptoms for either left or right heart failure [illegible] symptoms was too inadequate to make possible a fully certain classification.
[d] Not computed since there were fewer than 10 cases in the sample.

APPENDIX TABLE 24

TYPE OF CONGESTIVE HEART FAILURE AND DEGREE OF SHOCK, BY PERIOD OF ILLNESS: Number of Cases in the Total Sample and in the Control and Treated Groups Showing Various Types of Congestive Heart Failure and Maximum Shock of Various Degrees during the First Week and from the Second through the Sixth Week of Observation

Type of Congestive Heart Failure[a] and Maximum Degree of Shock Reported at Any Time	Number of Cases[b]					
	1st Week			2nd through 6th Week		
	Total Sample	Control Group	Treated Group	Total Sample	Control Group	Treated Group
Congestive Heart Failure						
No heart failure[c]	715	297	418	774	322	452
Left heart failure only	141	66	75	73	32	41
Right heart failure only	75	30	45	56	27	29
Both left and right heart failure	100	49	51	56	29	27
Total with symptoms	316	145	171	185	88	97
Total cases at beginning of the period	1031	442	589	959	410	549
Shock						
No shock	749	318	431	895	377	518
One degree of shock	82	35	47	5	2	3
Two degrees of shock	97	43	54	13	11	2
Three degrees of shock	45	17	28	5	2	3
Four degrees of shock	31	17	14	12	5	7
Degree of shock unknown	9	3	6	7	3	4
Total with symptoms	264	115	149	42	23	19
No report on symptoms	18	9	9	22	10	12
Total cases at beginning of the period	1031	442	589	959	410	549

[a] For definition, see footnote a, Table 66 of the text.

[b] For percentages based on these numbers, see Tables 66 and 67 of the text.

[c] Includes occasional cases for whom the reporting of symptoms was too inadequate to make possible a fully certain classification

APPENDIX TABLE 27

SEDIMENTATION RATE: Number of Cases in the Total Sample and in the Control and Treated Groups with Elevated Sedimentation Rate, by Period of Illness and Broad Age Groups

Period of Illness and Maximum Sedimentation Rate Reported	Number of Cases[a]								
	Total Sample			Control Group			Treated Group		
	All Ages[b]	Under 60	60 and Over	All Ages[b]	Under 60	60 and Over	All Ages[b]	Under 60	60 and Over
Total six week period									
Within normal limits:									
One or more tests in both periods	22	11	10	11	7	4	11	4	6
No test in one of two periods[c]	29	11	18	14	4	10	15	7	8
Elevated	905	505	399	380	207	173	525	298	226
No rates reported	75	35	39	37	15	21	38	20	18
Total cases	1031	562	466	442	233	208	589	329	258
First week									
Within normal limits	100	51	48	47	26	21	53	25	27
Elevated	689	392	296	284	56	128	405	236	168
No rate reported	242	119	122	111	51	59	131	68	63
Total cases at beginning of the period	1031	562	466	442	233	208	589	329	258
Second through sixth week:									
Within normal limits	49	31	17	20	11	9	29	20	8
Elevated	753	444	308	323	186	137	430	258	171
No rate reported	157	70	86	67	31	35	90	39	51
Total cases at beginning of period	959	545	411	410	228	181	549	317	230

[a] For percentages based on these counts, see Table 75 of the text.
[b] In some cases totals for all ages exceed sum of two subgroups since these subgroups exclude cases of unknown age
[c] Counted as within normal limits in Table 75 of the text

APPENDIX TABLE 26

DEGREE OF SHOCK, BY AGE AND TREATMENT GROUPS: Number and Percentage of Case *the Control and Treated Groups Developing Maximum Shock of Various Degrees during the Si Week Period of Observation, by Age and Treatment Groups*

Maximum Degree of Shock Reported at Any Time	Control Group								Treated Group							
	Al Age	Under 40	40–49	50–59	60–69	70–79	80–89	Age Unknown	All Ages	Under 40	40–49	50–59	60–69	70–79	80–89	Age Un-
	Number of Cases															
No shock	305	4	50	115	87	45	3	—	421	13	69	157	122	49	10	
One degree of shock	33	2	6	10	16	3	1	—	48	2	11	16	14	5	—	-
Two degrees of shock	47	2	8	15	16	5	1	—	56	2	8	24	12	7	2	
Three degrees of shock	18	1	5	4	4	3	—	1	28	—	2	9	12	4	1	-
Four degrees of shock	22	—	3	3	7	9	—	—	22	—	3	6	7	5	1	-
Degree of shock unknown	5	—	—	2	2	1	—	—	5	—	1	1	3	—	—	—
No report on shock	7	—	—	3	1	3	—	—	9	—	—	5	2	2	—	—
Total cases	442	9	72	152	133	70	5	1	559	17	94	218	172	72	14	[illegible]
	Percentage of Cases[a]															
No shock	70.1	—[b]	69.4	77.2	65.9	63.7	—[b]	—[b]	72.6	76.4	73.4	73.7	71.8	70.0	71.4	—
One degree of shock	8.7	—[b]	8.3	6.7	12.1	4.5	—[b]	—[b]	8.3	11.7	11.7	7.5	8.2	7.1	—	—
Two degrees of shock	10.8	—[b]	11.1	10.1	12.1	7.4	—[b]	—[b]	9.6	11.8	8.5	11.3	7.1	10.0	14.3	—
Three degrees of shock	4.1	—[b]	7.0	2.7	3.1	4.5	—[b]	—[b]	4.3	—	2.1	4.2	7.0	5.7	7.1	—
Four degrees of shock	5.1	—[b]	4.2	2.0	5.3	13.4	—[b]	—[b]	3.8	—	3.2	2.8	4.1	7.2	7.1	—
Degree of shock unknown	1.2	—[b]	—	1.3	1.5	1.5	—[b]	—[b]	.9	—	1.1	.5	1.8	—	—	—
Total cases	100.0	—[b]	100.0	100.0	100.0	100.0	—[b]	—[b]	100.0	100.0	100.0	100.0	100.0	100.0	100.0	—

Note: *Italics are used when percentages quoted are based on less than 50 cases since chance factors render such figures particularly unstable*

[a] Based on number of cases with a report on shock (total cases minus cases with no report on shock).

[b] Not computed since there were fewer than 10 cases in the sample.

APPENDIX TABLE 27

SEDIMENTATION RATE. Number of Cases in the Total Sample and in the Control and Treated Groups with Elevated Sedimentation Rate, by Period of Illness and Broad Age Groups

Period of Illness and Maximum Sedimentation Rate Reported	Number of Cases[a]								
	Total Sample			Control Group			Treated Group		
	All Ages[b]	Under 60	60 and Over	All Ages[b]	Under 60	60 and Over	All Ages[b]	Under 60	60 and Over
Total six-week period:									
Within normal limits									
One or more tests in both periods	22	11	10	11	7	4	11	4	6
No test in one of two periods[c]	29	11	18	14	4	10	15	7	8
Elevated	905	505	399	380	207	173	525	298	226
No rates reported	75	35	39	37	15	21	38	20	18
Total cases	1031	562	466	442	233	208	589	329	258
First week:									
Within normal limits	100	51	48	47	26	21	53	25	27
Elevated	689	392	296	284	56	128	405	236	168
No rate reported	242	119	122	111	51	59	131	68	63
Total cases at beginning of the period	1031	562	466	442	233	208	589	329	258
Second through sixth week:									
Within normal limits	49	31	17	20	11	9	29	20	8
Elevated	753	444	308	323	186	137	430	258	171
No rate reported	157	70	86	67	31	35	90	39	51
Total cases at beginning of period	959	545	411	410	228	181	549	317	230

[a] For percentages based on these counts, see Table 75 of the text

[b] In some cases totals for all ages exceed sum of two subgroups since these subgroups exclude cases of unknown age

[c] Counted as within normal limits in Table 75 of the text

APPENDIX TABLE 28

MAXIMUM LEUKOCYTE COUNTS: Number and Percentage of Cases in the Total Sample and in the Control and Treated groups with Maximum Leukocyte Counts at Various Levels during the Total Period, during the First Week, and from the Second through the Sixth Week of Observation

Level of Maximum Leukocyte Count Reported[a], [b]	Number of Cases: Total Six-Week Period: Total Sample	Number of Cases: Total Six-Week Period: Control Group	Number of Cases: Total Six-Week Period: Treated Group	Number of Cases: 1st Week: Total Sample	Number of Cases: 1st Week: Control Group	Number of Cases: 1st Week: Treated Group	Number of Cases: 2nd through 6th Week: Total Sample	Number of Cases: 2nd through 6th Week: Control Group	Number of Cases: 2nd through 6th Week: Treated Group	Percentage of Cases[c]: Total Six-Week Period: Total Sample	Percentage of Cases[c]: Total Six-Week Period: Control Group	Percentage of Cases[c]: Total Six-Week Period: Treated Group	Percentage of Cases[c]: 1st Week: Total Sample	Percentage of Cases[c]: 1st Week: Control Group	Percentage of Cases[c]: 1st Week: Treated Group	Percentage of Cases[c]: 2nd through 6th Week: Total Sample	Percentage of Cases[c]: 2nd through 6th Week: Control Group	Percentage of Cases[c]: 2nd through 6th Week: Treated Group
Below normal (3,500–4,400)	—	—	—	—	—	—	6	4	2	—	—	—	—	—	—	.8	1.2	.4
Normal range·																		
4,500 to 5,400	2	1	1	5	2	3	11	7	4	.2	.2	.2	.5	.5	.6	1.4	2.1	.9
5,500 to 6,400	9	4	5	21	5	19	47	20	27	.9	.9	.8	2.6	1.3	3.6	5.9	5.9	5.9
6,500 to 7,400	28	10	18	31	16	18	71	22	49	2.7	2 3	3.0	3.7	4.0	3.4	8.9	6.5	10.7
7,500 to 8,400	52	18	34	52	18	34	116	41	72	5.1	4.1	5.8	5.6	4.6	6.4	14.5	13.0	15.7
8,500 to 9,400	76	38	38	71	34	37	120	55	65	7.4	8.7	6.5	7.7	8.6	6.9	15.1	16.3	14.1
Total in normal range	167	71	96	186	75	111	365	148	217	16.3	16.2	16.3	20.1	19.0	20.9	45.8	43.8	47.3
Above normal																		
9,500 to 10,400	105	42	63	88	38	50	110	40	70	10.2	9.6	10.7	9.5	9.6	9.4	13.8	11.8	15.2
10,500 to 11,400	107	48	59	96	38	58	89	41	48	10.4	10.9	10.0	10.4	9.6	10.9	11.2	12.1	10.5
11,500 to 12,400	112	45	67	100	46	54	62	22	40	10.9	10.2	11.4	10.8	11.6	10.1	7.8	6.5	8.7
12,500 to 13,400	88	37	51	67	28	39	41	21	20	8.6	8.4	8.7	7.2	7.1	7.3	5.5	7.1	4.4
13,500 to 14,400	94	36	58	82	30	52	35	20	15	9.1	8.2	9.9	8.9	7.6	9.8	4.4	5.0	3.3
14,500 to 15,400	67	27	40	56	25	31	26	13	13	6.5	6.1	6.8	6.0	6.3	5.8	3.3	3.8	2.9
15,500 to 16,400	54	25	29	52	23	29	11	5	6	5.3	5.7	4.0	5.6	5.8	5.5	1.4	1.5	1.3
16,500 to 17,400	49	20	29	39	17	22	10	4	6	4.8	4.6	4.9	4.2	4.3	4.1	1.3	1.2	1.3
17,500 to 18,400	43	19	24	37	16	21	12	4	8	4.2	4.3	4.1	4 0	4.1	3.9	1.5	1.2	1.8
18,500 to 19,400	31	16	15	26	12	14	6	4	2	3.0	3.6	2.6	2.8	3.0	2.6	.7	1.2	.4
19,500 to 20,400	19	7	12	18	7	11	2	—	2	1.8	1.6	2.0	1 9	1.8	2.1	.2	—	.4
20,500 to 21,400	17	9	8	17	9	8	4	1	3	1.6	2.0	1.4	1.8	2.3	1.5	.5	.3	.7
21,500 to 22,400	15	6	9	15	6	9	3	1	2	1 5	1.4	1.5	1.6	1.5	1.7	.4	.3	.1

22,500 to 23,400	11	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
23,500 to 24,400	13	5	8	9	2	7	4	3	1	1.3	1.1	1.4	1.0	.5	1.3	.5	.9	.2
24,500 to 25,400	5	2	3	4	2	2	—	—	—	.5	.5	.5	.4	.5	.4	—	—	—
25,500 to 30,400	23	13	10	23	13	10	2	1	1	2.2	3.0	1.7	2.5	3.3	1.0	.2	.3	.2
30,500 to 35,400	5	3	2	1	1	—	4	2	2	.5	.7	.3	.1	.3	—	.5	.6	.4
35,500 to 40,400	2	2	—	1	1	—	1	1	—	.2	.5	—	.1	.3	—	.1	.3	—
Total above normal range	860	368	492	741	320	421	426	186	210	83.7	83.8	83.7	79.9	81.0	79.1	53.4	55.0	52.3
Total cases with reading in period	1027	439	588	927	395[b]	532[b]	797	338[b]	459[b]	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total cases at beginning of the period	1031	442	589	1031	442	589	959	410	549	—	—	—	—	—	—	—	—	—

[a] Readings were classified to the nearest 100 prior to tabulation.

[b] Maximums are influenced by the number of readings reported. In the control group during the first week, 188 cases had only one reading reported; 112, two readings, and 95, three or more readings. During the second through the sixth week, 76 cases had only one reading; 78, two readings; and 184, three or more. In the treated group during the first week, 219 cases had only one reading; 169 cases, only two readings; and 114, three or more. For later weeks this group contained 118 cases with one reading, 96 cases with two, and, 251 cases with three or more.

[c] Based on number of cases with leukocyte reading in the period.

APPENDIX TABLE 29

POLYCYTHEMIA CASES: Essential Facts on Patients in this Study Known to Have Had Polycythemia

Type of Patient		Hematological Data					Anticoagulant Therapy		Death or Complication during Six Weeks	Comments
Age and Sex	Treatment Group	Day of Illness[a]	Hgb (gm.)	RBC	Hematocrit (%)	Venesection	Average Dose of Dicumarol (mg)	Days of Illness Treated		
Female, age 82	Odd-day, treated	1	16.0	6.2	56	None	22	2 to 32	None	Infarct 6 years before this illness with failure intermittently since, hypertension *Diabetes and polycythemia were discovered during this illness. No record of either in the history* Developed bronchopneumonia after onset of this illness. Auricular fibrillation and frequent premature beats throughout illness. Diagnosis of polycythemia secondary to dehydration and cardiac failure Patient living and well at end of six weeks Died after 7 weeks while asleep at home. (No diagnosis reported, patient apparently not under anticoagulants at the time)
		3	17.5	6.8	62					
		6	17.2		62					
		15	18.5	7.0	62					
		29	14.7	5.2	47					
Male, age 64	Odd-day, treated	2		5.7	52	None	75	1 to 21	None	*Polycythemia vera listed in patient's history but no details given.* Diabetes mellitus reported in history. Diagnosis of polycythemia reported during this illness as mild
		5	17.9	6.2	50					
		33	17.0	6.4	47					
		48	14.0	5.0	43					
Female, age 51	Even-day, treated (see comments)	4	24.0	11.6	71	350 cc.	56	2 to 42	None	Two years prior to the present illness, the patient's Hgb. was 15.0, RBC, 7.4, hematocrit, 52 Patient given anticoagulants as exception because of polycythemia. *Polycythemia rubra vera of 10 years duration* Two years before this illness patient had cerebral accident with right hemianopsia and contraction of visual fields Patient was continued on anticoagulants at home. Was readmitted to hospital, 61 days after onset of illness studied, with quinidine therapy for bigeminy On the 71st day while still on anticoagulants, she had posterior myocardial infarction and died within 3 hours.
		6	20.0	10.0	70	350 cc.				
		8	16.0	6.2	46					
		19	14.5			350 cc.				
		24	14.6	4.5						
		61	16.5	6.1		350 cc				
		66	18.0	5.8	52					

Type of Patient		Hematological Data					Anticoagulant Therapy		Death or Complication during Six Weeks	Comments
e and Sex	Treatment Group	Day of Illness[a]	Hgb (gm.)	RBC	Hematocrit (%)	Venesection	Average Dose of Dicumarol (mg.)	Days of Illness Treated		
ale e 58	Even-day, control (see comments)	3 4 5 6 8 12 15 22 27 34	20 9 19 2 14.6 11 2 15 8 13 8 11 4	7 5 5 6 4 7 3 9 4 9 3 4	81	 500 cc. 500 cc. 500 cc.	86	13 to 21	Pulmonary embolus 13th day No death	Treated after developing pulmonary embolus. *Polycythemia vera diagnosed during this admission* Uremia (NPN 86) Operative procedure for closure of slough. Dicumarol discontinued because of subsequent moderate bleeding into area. No follow-up after end of second month.
age	Even-day, control	1-94[b]	16 5 to 18 7[b]	5.0 to 5 7[b]	45 to 50[b]	None	None	None	None	*Twenty years prior to present illness polycythemia was diagnosed and patient apparently had some x-ray therapy at that time which resulted in a permanent remission.* There was, however, evidence of polycythemia during the present period of hospitalization. Patient suffered from gout and liver damage during this illness. Hospital stay prolonged because of marked leg weakness secondary to Parkinsonism.

Data for periods beyond six-week study period are included where reported
Relation to study period uncertain since exact dates of tests were not reported The readings for Hgb., RBC, and hematocrit
esent the range for the entire period of hospitalization

APPENDIX TABLE 30

HOLESTEROL TEST METHODS. Methods Used by Participating Hospitals in Performing Cholesterol Tests for the Study and Ranges Considered Normal at Time Tests Were Performed

Hospital	Method Used in Testing Cholesterol Level	Normal Range (in mg %)
levue, New York	Digitonin precipitation and colorimetric analysis	150-250
h Israel, Boston	Bloor method	
cinnati General	Bloor method	175-275
reland City	Myers-Wardell method	180-250
nry Ford, Detroit	Bloor-Sackett method	140-190
kson Memorial, Miami	Neuschloss technique	140-280
keside, Cleveland	Modification of Myers and Wardell method	150-230
ssachusetts General, Boston	Bloor method	150-250
chael Reese, Chicago	Schoenheimer-Sperry	150-230
unt Zion, San Francisco	Bloor method	120-300
e New York Hospital, New York	Bloor method	150-250
nnsylvania, Philadelphia	Bloor's alcohol-ether method	175-275
ter Bent Brigham, Boston	Modification of Bloor method	200-330
ode Island, Providence	S[illegible]	
n Francisco, Sa[illegible]		

APPENDIX TABLE 31

MISCELLANEOUS DISEASES AND CONDITIONS COMPLICATING THE ILLNESS: *Number of Cases in the Total Sample and in the Control and Treated Groups Reported to Have Had, or Probably Had, Miscellaneous Diseases or Conditions of the Various Body Systems during the Six-Week Period of Illness Observed*

Diagnoses Reported	Number of Cases		
	Total Sample	Control Group	Treated Group
Diseases of the Cardiovascular System			
Rheumatic heart disease	3	1	2
Syphilitic heart disease	2	2	—
Subacute bacterial endocarditis	1	—	1
Pericarditis	10	5	5
Aneurysm	2	—	2
Diseases of the Respiratory Tract and Lungs			
Upper respiratory infections	6	—	6
Bronchial infections:			
Bronchitis	2	—	2
Bronchiectasis	3	—	3
Asthma (bronchial and cardiac asthma not always clearly differentiated)	8	4	4
Pulmonary diseases:			
Consolidation, lung	1	1	—
Pneumonia, total	48	22	26
Pneumonia, unqualified	30	14	16
Bronchopneumonia	18	8	10
Pulmonary emphysema	4	2	2
Atelectasis	3	—	3
Pulmonary fibrosis	2	—	2
Cancer of lung	1	—	1
Pre-existing pulmonary infarcts	1	1	—
Pleural diseases:			
Pleurisy with effusion	1	1	—
Peripleuritis	1	1	—
Diseases of the Gastrointestinal Tract			
Esophageal varices	1	1	—
Pylorospasm	1	—	1
Hiatal hernia	5	4	1
Peptic ulcer (gastric, pyloric, duodenal, unspecified)	19	9	10
Diseases of the Gastrointestinal Tract—*Continued*			
Gastric resection, subtotal previous	1	—	1
Cancer:			
Stomach	1	—	1
Colon (including cecum, sigmoid)	2	—	2
Pancreatitis	2	1	1
Diseases of the Liver			
Jaundice, etiology not specified	7	4	3
Cirrhosis	1	1	—
Cancer	1	—	1
Liver disease, type not specified	8	4	4
Fatty liver	1	—	1
Diseases of the Gallbladder			
Cholecystitis	2	1	1
Gallstones (cholelithiasis)	5	3	2
Cholangitis	1	1	—
Gallbladder disease, type *not specified*	4	3	1
Cholecystectomy (see also list of operations during the illness)	20	10	10
Diseases of the Kidneys and Genitourinary System			
Renal disease:			
Uremia (or azotemia)	70	32	38
Nephritis (and perinephritis)	2	—	2
Hydronephrosis	1	—	1
Nephrolithiasis (renal calculi)	4	—	4
Previous nephrectomy	2	—	2
Renal disease, type not specified (except hematuria)	11	4	7
Urinary tract infections:			
Pyelitis and pyelonephritis	6	1	5
Cystitis	5	1	4
Pyuria	3	1	2
Pyoureter	1	—	1
Genitourinary infections, *type not specified* (except hematuria)	8	2	6

...noses Reported	Number of Cases		
	Total Sample	Control Group	Treated Group
...ses of the Kidneys and Genitourinary System—*Continued*			
... calculi	1	—	1
(or urinary reten-	4	1	3
...es of the prostate:			
...tatic hypertrophy	7	2	5
...cer of the prostate	1	—	1
...statitis	2	—	2
...static obstruction	2	—	2
...statectomy, previous	1	—	1
...ansurethral resection, previous	1	—	1
...udectomy, previous	1	—	1
...eases of the Metabolism and the Endocrine Glands			
...seases of the thyroid			
Hypothyroidism and myxedema	5	2	3
Thyroidectomy, previous	4	4	—
Goiter	2	—	2
Hyperthyroidism	1	1	—
Adenoma	1	1	—
Diseases of the parathyroid			
Hyperparathyroidism	1	—	1
Diabetes mellitus	100	44	56
Gout	3	2	1
Diseases of the Brain and Nervous System			
Hemiparesis and hemiplegia	12	7	5
Aphonia	1	1	—
Parkinsonism	3	2	1
Epilepsy	1	—	1
Migraine	1	—	1
Neuroses and psychoses			
Organic psychoses	1	—	1
Other psychoses and neuroses (psychiatric symptoms, anxiety, psychotic episodes)	4	3	1
Delirium and coma (cerebral anoxemia, coma, irrational episodes, delirium, confusion)	6	1	5
Sympathectomy, previous	2	—	2
Herniated intervertebral			

Diagnoses Reported	Number of Cases		
	Total Sample	Control Group	Treated Group
Diseases of the Blood			
Anemia .. .	9	3	6
Polycythemia	5	2	3
Septicemia	1	—	1
Diseases of the Skin			
Erythema nodosa	1	—	1
Erythema multiforme (generalized)	1	—	1
Psoriasis	1	—	1
Furunculosis	1	—	1
Rashes (miscellaneous)	6	2	4
Diseases of the Muscular and Skeletal Systems			
Rheumatism, arthritis and arthralgia (including periarthritis, periarthralgia, osteoarthritis and synovitis)	12	4	8
Fractures, recent, unhealed	4	1	3
Abscesses or localized infections of skin or muscles	5	3	2
Gangrene	2	—	2
Cellulitis	1	—	1
Kyphoscoliosis	1	—	1
Osteomyelitis	1	—	1
Paget's disease	1	1	—
Diseases, Miscellaneous			
Conditions of the eye			
Conjunctivitis	2	1	1
Hemianopsia	1	1	—
Cancer (cases not listed under systems)			
Mouth	1	1	—
Breast	1	—	1
Location not specified	2	—	2
Barbital poisoning	1	—	1
Alcoholism	6	1	5
Syphilis	10	6	4
Operations during the First Six Weeks after the Attack			
Ligation of a vein	2	2	—
Embolectomy	1	1	—
Nephrectomy	1	1	—
Cholecystostomy and chole-	1	1	—
dochoduodenostomy	1	1	—
Supracondylar amputation	1	1	—

APPENDIX TABLE 32

CONDITIONS OF OBSERVATION AND CARE: *Total Days and Average Number of Days Spent by Patients in the Control and Treated Groups under Various Conditions of Observation and Care*

Status of Patient	Total Patient-Days Reported		Average Number of Days per Patient	
	Control Group (442 Patients)	Treated Group (589 Patients)	Control Group	Treated Group
Days prior to diagnosis[a]	1,203	1,535	2.7	2.6
Days prior to beginning of anticoagulants	—[b]	2,253[c]	—[b]	3.9
Days prior to admission to hospital[d]	1,180	1,408	2.7	2.4
Days in hospital[e]	12,470	17,651	28.2	30.0
[illegible]	2,119	2,792	4.8	4.7
[illegible]	2,089	2,771	4.7	4.7
Not covered by medical follow-up	30	21	.1	—[f]
Total days	15,769	21,854	35.7	37.1

[a] Categories overlap counts on hospitalization.

[b] Since most control patients received no anticoagulants, counts *in these categories are omitted.*

[c] Counts omit the 12 patients in the treated group not receiving anticoagulants because of contraindications.

[d] The day of the attack was counted as a full day (premonitory symptoms often preceded attack)

[e] The day of admission and the day of discharge were allocated one-half to time outside the hospital (before and after respectively) and one-half to time in the hospital.

[f] Less than .05

APPENDIX TABLE 33

TYPE OF HOSPITAL SERVICE, BY HOSPITAL: Number of Cases in the Total Sample and in the Control and Treated Groups Receiving Ward and Private or Semiprivate Care during the Six-Week Period of Observation and the Percentage of Cases Receiving Ward Care Only, by Hospital

Hospital	Number of Cases												Percentage of Cases Receiving Ward Care Only		
	Total Sample				Control Group				Treated Group						
	Total Cases	Cases Receiving—			Total Cases	Cases Receiving—			Total Cases	Cases Receiving—					
		Private or Semi-private Service	Ward Service	Two or More Types[a]		Private or Semi-Private Service	Ward Service	Two or More Types[a]		Private or Semi-private Service	Ward Service	Two or More Types[a]	Total Sample	Control Group	Treated Group
Bellevue, New York	49	—	49	—	21	—	21	—	28	—	28	—	100	*100*	*100*
Beth Israel, Boston	57	—	50	7	32	—	31	1	25	—	19	6	88	*97*	*76*
Cincinnati General	101	6	94	1	48	3	45	—	53	3	49	1	93	*94*	*93*
Cleveland City	23	—	23	—	10	—	10	—	13	—	13	—	*100*	*100*	*100*
Henry Ford, Detroit	126	111	—	15	48	45	—	3	78	66	—	12	0	0	*0*
Jackson Memorial, Miami	43	—	43	—	19	—	19	—	24	—	24	—	100	*100*	*100*
Lakeside, Cleveland	102	46	56	—	34	10	24	—	68	36	32	—	55	71	*47*
Massachusetts General, Boston	26	—	26	—	9	—	9	—	17	—	17	—	*100*	*100*	*100*
Michael Reese, Chicago[b]	130	120	10	—	59	54	5	—	71	66	5	—	8	9	*7*
Mount Zion, San Francisco	45	29	10	6	14	10	3	1	31	19	7	5	22	*21*	23
The New York Hospital, New York	69	—	67	2	29	—	28	1	40	—	39	1	97	*97*	*98*
Pennsylvania, Philadelphia	40	—	40	—	21	—	21	—	19	—	19	—	100	*100*	*100*
Peter Bent Brigham, Boston	47	8	39	—	17	2	15	—	30	6	24	—	83	*88*	*80*
Rhode Island, Providence	115	46	69	—	54	26	28	—	61	20	41	—	*60*	*52*	*67*
San Francisco, San Francisco	25	—	25	—	7	—	7	—	18	—	18	—	*100*	*100*	*100*
Veterans Administration, Bronx, New York	33	—	33	—	20	—	20	—	13	—	13	—	100	*100*	*100*
Total cases	1031	366	634	31	442	150	286	6	589	216	343	25	*62*	*65*	*59*

APPENDIX TABLE 34

IVATE DUTY NURSING CARE: Number and Percentage of Patients in the Total Sample and in he Control and Treated Groups Receiving Private Duty Nursing Care at Some Time during Their Illness, by Severity of Illness at Onset and Type of Hospital Service Received

Type of Service and Severity at Onset	Total Sample			Control Group			Treated Group		
	Total Cases with Report on Nursing Service	Cases with Private Duty Nurse		Total Cases with Report on Nursing Service	Cases with Private Duty Nurse		Total Cases with Report on Nursing Service	Cases with Private Duty Nurse	
		Number	Per Cent		Number	Per Cent		Number	Per Cent
Ward cases[a]									
Severe	163	13	8.0	63	7	11.1	100	6	6.0
Mild or moderate	420	4	1.0	202	3	1.5	218	1	.5
Total ward	583	17	2.9	265	10	3.8	318	7	2.2
Private or semiprivate cases.									
Severe	97	38	39.2	35	9	25.7	62	29	46.8
Mild or moderate	234	34	14.5	100	9	9.0	134	25	18.7
Total private or semiprivate	331	72	21.8	135	18	13.3	196	54	27.6
All cases[a]									
Severe	269	53	19.7	104	16	15.4	165	37	22.4
Mild or moderate	675	40	5.9	302	12	4.0	373	28	7.5
Total cases	944	93	9.9	406	28	6.9	538	65	12.1

[a] Cases with mixed types of service are not included either in the ward or private and semiprivate categories but are included in the "All Cases" figures. Totals therefore exceed the sum of the components cited.

APPENDIX TABLE 35

DRUGS RECEIVED: Number of Cases in the Total Sample and in the Control and Treated Groups Receiving Various Types of Drugs and Therapeutic Agents other than Anticoagulants during the Six-Week Period of Observation

Type of Drug[a]	Number of Cases Receiving Drug[b, c]		
	Total Sample	Control Group	Treated Group
Narcotics....	651	266	385
Oxygen (by tent, mask or nasal catheter)	592	248	344
Hypnotics and sedatives:			
Barbiturates .	320	130	190
Nonbarbiturates	49	15	34
Total hypnotics and sedatives.	339[d]	134[d]	205[d]
Atropine and antispasmodics	327	139	188
Digitalis and digitaloids	280	128	152
Quinidine	253	100	153
Xanthines	245	104	141
Antibiotics and sulfonamides			
Penicillin	146	76	70
Streptomycin	8	4	4
Sulfonamides	22	12	10
Total antibiotics and sulfonamides	160[d]	83[d]	77[d]
Diuretics..	147	69	78
Salicylates.	112	39	73
Vitamin K	82	10	72
Nitrites	76	33	43
Blood and blood substances.			
Fresh whole blood	16	3	13
Washed erythrocytes	2	2	—
Plasma..	21	10	11
Total blood and blood substances	33[d]	12[d]	21[d]
Cathartics[e]	17	9	8
Sympathomimetic drugs	13	5	8
Rutin	7	3	4
Vitamin C.	7	1	6
Coramine..	5	1	4

[a] Counts exclude drugs of no interest to the study and drugs received by only one or two persons.

[b] Reports of drugs received are undoubtedly incomplete, particularly for the periods before hospitalization and after discharge.

[c] For percentages based on these counts, see Table 88 of the text.

[d] Total count is less than the sum of the components because cases receiving two or more subtypes are counted only once.

[e] Probably underreported. Excludes mineral oil.

APPENDIX TABLE 36

[illegible]NTICOAGULANT THERAPY, BY WEEK OF ILLNESS: Number of Days and Percentage of Total Days in the Control and Treated Groups When Patients Were under Anticoagulant Therapy, by Week of Illness and Stage of Therapy

Week of Illness and Treatment Group	Number of Survivors at Beginning of Week	Number of Days Observed: Total Days Observed	Days before Beginning of Therapy (or for Patients Never Treated)	Days under Anticoagulant Therapy: [illegible]py	[illegible]apy	[illegible] Last Dose	[illegible] Dose*	Days [illegible] of [illegible]mination during [illegible]erapy	Days under Anticoagulant Therapy as Percentage of Total Days Observed: Total [illegible]	Days [illegible]	Days between [illegible]	Days [illegible]
Control group												
First week	442	3,023	2,985	38	28	10	—	—	1.3	.9	.4	—
Second week	410	2,759	2,661	98	29	69	—	—	3.6	1.1	2.5	—
Third week	378	2,595	2,457	138	14	124	—	—	5 3	.5	4.8	—
Fourth week	365	2,506	2,342	161	16	136	9	3	6 4	6	5.4	.4
Fifth week	351	2,452	2,262	166	11	135	20	24	6 8	5	5 5	8
Sixth week	349	2,434	2,233	154	8	137	9	47	6.3	3	5.6	.4
Total, all weeks	442	15,769	14,940	755	106	611	38	74	4.8	.7	3.9	.2
Treated group												
First week	589	4,038	1,701	2,336	1,379	948	9	1	57 9	34 2	23.5	.2
Second week	549	3,738	302	3,423	265	3,138	20	13	91.6	7.1	84.0	.5
Third week	518	3,588	128	3,413	45	3,282	86	47	95.1	1.2	91.5	2.4
Fourth week	508	3,525	67	3,183	11	2,871	301	275	90.3	3	81.5	8.5
Fifth week	500	3,493	50	2,514	7	1,816	691	929	72 0	.2	52 0	19 8
Sixth week	497	3,472	42	1,339	5	931	403	2,091	38 6	.2	26 8	11.6
Total, all weeks	589	21,854	2,290	16,208	1,712	12,986	1,510	3,356	74 1	7.8	59.4	6.9

* If a sufficient number of prothrombin times were reported after the last dose, days were counted as under therapy until these times returned to 17 seconds or less (58% or more) on the standardized curve.

APPENDIX TABLE 37

COMPLICATIONS AND DEATHS, BY HOSPITAL: Number of Cases Developing Thromboembolic Complications, Number of Such Complications and Number of Cases Dying in the Control and Treated Groups, by Hospital

Hospital	Total Cases Observed		Number of Cases Developing Thromboembolic Complications		Number of Thromboembolic Complications		Number of Cases Dying	
	Control Group	Treated Group	Control Group	Treated Group	Control Group*	Treated Group	Control Group*	Treated Group
Bellevue, New York	21	28	4	2	4	4	7	5
Beth Israel, Boston	32	25	8	2	12	2	3	5
Cincinnati General	48	53	15	5	23	6	18	8
Cleveland City	10	13	2	—	3	—	5	4
Henry Ford, Detroit	48	78	13	8	23	11	5	12
Jackson Memorial, Miami	19	24	7	4	11	5	2	5
Lakeside, Cleveland	34	68	6	9	9	10	12	7
Massachusetts General, Boston	9	17	2	2	2	3	1	6
Michael Reese, Chicago	59	71	14	7	22	8	14	9
Mount Zion, San Francisco	14	31	3	3	4	4	2	5
The New York Hospital, New York	29	40	11	4	16	6	4	4
Pennsylvania, Philadelphia	21	19	6	3	8	3	3	1
Peter Bent Brigham, Boston	17	30	2	1	2	1	2	5
Rhode Island, Providence	54	61	17	8	25	8	13	11
San Francisco, San Francisco	7	18	1	5	1	5	2	6
Veterans Administration, Bronx, New York	20	13	4	1	7	1	3	1
All hospitals	442	589	115	64	172	77	96	94

* Counts have not been corrected for exceptions in treatment.

APPENDIX TABLE 38

SINGLE AND MULTIPLE COMPLICATIONS: Number and Percentage of Cases Developing No Thromboembolic Complications or One, Two, Three, or Four Such Complications in the Control and Treated Groups during the Six-Week Period of Observation

Number of Complications per Case	Control Group				Treated Group	
	As Reported		Corrected for Exceptions in Treatment*		Number of Cases	Per Cent of Cases
	Number of Cases	Per Cent of Cases	Number of Cases	Per Cent of Cases		
None	327	74.0	327.0	74 0	525	89.1
One	75	16 9	69.9	15 8	54	9.2
Two	26	5.9	23.5	5.3	7	1.2
Three	11	2.5	18.4	4.2	3	.5
Four	3	.7	3.2	.7	—	—
Total cases	442	100 0	442.0	100 0	589	100 0

* For method of correction, see Appendix B

APPENDIX TABLE 39

TYPE AND LOCATION OF COMPLICATIONS: Total Number of Thromboembolic Complications Developing in the Control and Treated Groups during the Six-Week Period of Observation and Average Number of Such Complications per Hundred Cases, by Type and Location and Status of Anticoagulant Therapy at Time Complication Developed

Type and Location of Complication	Number of Thromboembolic Complications											
	Total Number						Average Number per 100 Cases					
	Control Group (442 Cases)		Treated Group (589 Cases)				Control Group		Treated Group			
				Complications Occurring—						Complications Occurring—		
	Total as Re- [illegible]	Total Cor-rected [illegible]	Total during [illegible]	While [illegible] apy[b]	During [illegible] apy	After [illegible] apy[c]	Total as Re- [illegible]	Total Cor-rected [illegible]	Total during Six-Week Period	While Patient Not under Antico-agulant Ther-apy[b]	During First Three Days of Antico-agulant Ther-apy	After Third Day of Antico-agulant Ther-apy[c]
Intracardiac Complications												
Secondary myocardial infarctions.												
Extensions.	40	43 0	19	3	1	15	9.0	9.7	3.2	.5	.2	2.5
New infarctions	25	26 9	11	2	—	9	5 7	6 1	1.9	.3	—	1.6
Total intracardiac complications	65	69.9	30	5	1	24	14 7	15 8	5 1	.8	.2	4.1
Extracardiac Complications												
Emboli												
Pulmonary	48	51.5	28	13	6	9	10 9	11.6	4.8	2.2	1.0	1.6
Cerebral[d]	20	21 6	4	2	—	2	4 5	4.9	.7	.4	—	3
Peripheral and visceral[e]	11	11.8	3	—	2	1	2 5	2.7	.5	—	.3	.2
Venous thromboses	28	30 1	12	7	1	4	6 3	6.8	2.0	1.2	.2	.6
Total extracardiac complications	107	115.0	47	22	9	16	24 2	26 0	8 0	3 8	1.5	2.7
Total, all thromboembolic complications	172	184 9	77	27	10	40	38.9	41.8	13.1	4.6	1.7	6.8

[a] For method of correction, see Appendix B

[b] For definition of category, see footnote c of Appendix Table 42

[c] For definition of category, see footnote d of Appendix Table 42

[d] See footnote b, Table 96 of the text

[e] See footnote c, Table 96 of the text

APPENDIX TABLE 40

COMPLICATIONS, BY WEEK OF ILLNESS: Total Number of Thromboembolic Complications the Control and Treated Groups and Average Number of Such Complications per Hundred Survivors at the Beginning of Each Week, by Week of Illness and Status of Anticoagulant Therapy at Time Complication Developed

Week of Illness	Number of Survivors from Previous Week			Number of Thromboembolic Complications[b]											
	Control Group			Total Number						Average Number per 100 Survivors from Previous Week					
				Control Group		Treated Group				Control Group		Treated Group			
							Complications Occurring—						Complications Occurring—		
	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Total	While Patient Not under Anticoagulant Therapy[c]	During First Three Days of Anticoagulant Therapy	After Third Day of Anticoagulant Therapy[c]	As Reported	Corrected for Exceptions in Treatment[a]	Total	While Patient Not Under Anticoagulant Therapy[c]	During First Three Days of Anticoagulant Therapy	Afte Third Day o Antico agulan Ther- apy[c]
First week ..	442	442.0	589	44	45.2	18	9	5	4	10.0	10.2	3.1	1.5	.9	.7
Second week..	410	409.0	549	55	58.4	27	10	5	12	13.4	14 3	4 9	1.8	.9	2 2
Third week..	378	374.7	518	32	35.2	12	3	—	9	8.5	9.4	2.3	.6	—	1.7
Fourth week.	365	360.3	508	20	22.3	5	—	—	5	5.5	6 2	1.0	—	—	1.0
Fifth week	351	344.4	500	8	9.2	4	1	—	3	2.3	2 7	.8	.2	—	.6
Sixth week.. .	349	342.0	497	8	9.2	4	2	—	2	2.3	2.7	.8	.4	—	.4

[a] For method of correction, see Appendix B.

[b] Counts exclude 5 complications in the control group (or 5 4 when corrected for exceptions in treat ment) and 7 complications in the treated group for which the date of occurrence is unknown Of thos in the treated group, 2 occurred while the patient was not under anticoagulants and 5 others, after th 3rd day of anticoagulant therapy.

[c] For definition of categories, see footnotes c and d of Appendix Table 42.

APPENDIX TABLE 41

CASES DEVELOPING COMPLICATIONS, BY AGE: Number and Percentage of Cases in the Control and Treated Groups Developing One or More Thromboembolic Complications during the Six-Week Period of Observation, by Age and Status of Anticoagulant Therapy at Time of First Complication

Age Group	Total Cases Observed: Control Group	Total Cases Observed: Treated Group	Number of Cases: Control Group—Total	Number of Cases: Treated Group: Total	Number of Cases: Treated Group: First Complication Occurring—While [illegible] apy[b]	Number of Cases: Treated Group: First Complication Occurring—During [illegible]	Number of Cases: Treated Group: First Complication Occurring—[illegible]	Percentage of Cases: Control Group—Total	Percentage of Cases: Treated Group: Total during [illegible]	Percentage of Cases: Treated Group: First Complication Occurring—While Patient [illegible]	Percentage of Cases: Treated Group: First Complication Occurring—During First [illegible]	Percentage of Cases: Treated Group: First Complication Occurring—After Third [illegible]
Under 40	9	17	2	2	1	—	1	—[d]	*11.8*	*5.9*	—	*5.9*
40–49	72	94	16	10	3	2	5	22.2	10.6	3.2	2.1	5.3
50–59	152	218	42	22	9	2	11	27.6	10.1	4.1	.9	5.1
60–69	133	172	32	18	4	2	12	24.1	10.5	2.3	1.2	7.0
70–79	70	72	22	10	3	1	6	31.4	13.9	4.2	1.4	8.3
80–89	5	14	1	2	1	—	1	—[d]	*14.3*	*7.2*	—	*7.1*
Age unknown	1	2	—	—	—	—	—	—[d]	—[d]	—[d]	—[d]	—[d]
All ages	442	589	115	64	21	7	36	26.0	10.9	3.6	1.2	6.1

Note: *Italics are used when percentages quoted have less than 50 cases* [illegible]

[illegible]

[a] Includes [illegible] developing a first complication after the last dose of anticoagulants before prothrombin time had returned to normal

[d] Not reported since there were less than 10 cases in the sample.

APPENDIX TABLE 40

COMPLICATIONS, BY WEEK OF ILLNESS: Total Number of Thromboembolic Complications in the Control and Treated Groups and Average Number of Such Complications per Hundred Survivors at the Beginning of Each Week, by Week of Illness and Status of Anticoagulant Therapy at Time Complication Developed

Week of Illness	Number of Survivors from Previous Week			Number of Thromboembolic Complications[b]											
	Control Group			Total Number						Average Number per 100 Survivors from Previous Week					
				Control Group		Treated Group				Control Group		Treated Group			
							Complications Occurring—						Complications Occurring—		
	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Total	While Patient Not under Anticoagulant Therapy[c]	During First Three Days of Anticoagulant Therapy	After Third Day of Anticoagulant Therapy[c]	As Reported	Corrected for Exceptions in Treatment[a]	Total	While Patient Not Under Anticoagulant Therapy[c]	During First Three Days of Anticoagulant Therapy	After Third Day of Anticoagulant Therapy[c]
First week ..	442	442 0	589	44	45 2	18	9	5	4	10 0	10 2	3.1	1.5	.9	.7
Second week.	410	409.0	549	55	58.4	27	10	5	12	13.4	14.3	4 9	1.8	.9	2 2
Third week .	378	374.7	518	32	35.2	12	3	—	9	8.5	9 4	2.3	.6	—	1.7
Fourth week .	365	360.3	508	20	22.3	5	—	—	5	5.5	6 2	1.0	—	—	1 0
Fifth week	351	344.4	500	8	9.2	4	1	—	3	2.3	2.7	.8	.2	—	.6
Sixth week .	349	342 0	497	8	9.2	4	2	—	2	2.3	2.7	.8	.4	—	.4

[a] For method of correction, see Appendix B.

[b] Counts exclude 5 complications in the control group (or 5.4 when corrected for exceptions in treatment) and 7 complications in the treated group for which the date of occurrence is unknown. Of those in the treated group, 2 occurred while the patient was not under anticoagulants and 5 others, after the 3rd day of anticoagulant therapy.

[c] For definition of categories, see footnotes c and d of Appendix Table 42.

APPENDIX TABLE 43

TYPE AND LOCATION OF COMPLICATIONS, BY AGE: Number of Thromboembolic Complications of Various Types and Locations and Average Number per Hundred Cases Occurring in the Control and Treated Groups during the Six-Week Period of Observation among Patients under Sixty Years of Age and Corresponding Data for Patients Sixty Years of Age and Over

Type and Location of Complication	Number of Thromboembolic Complications[a]											
	Total Number						Average Number per 100 Cases					
	Control Group				Treated Group		Control Group				Treated Group	
	Total as Reported		Total Corrected for Exceptions in Treatment[b]				Total as Reported		Total Corrected for Exceptions in Treatment[b]			
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Intracardiac Complications												
Secondary myocardial infarctions.												
Extensions.	20	20	21.7	21.3	12	7	8.6	9.6	9.3	10.2	3.7	2.7
New infarctions .	11	14	11.9	15 0	6	5	4.7	6.7	5.1	7.2	1.8	1.9
Total intracardiac complications	31	34	33.6	36 3	18	12	13.3	16.3	14.4	17.4	5.5	4.6
Extracardiac Complications												
Emboli:												
Pulmonary	25	23	26.9	24.6	13	15	10 7	11 0	11.6	11.8	4.0	5.8
Cerebral[c]	8	12	8 7	12.9	2	2	3.4	5.8	3.7	6.2	.6	.8
Peripheral and visceral[d].	4	7	4 5	7.3	2	1	1.7	3.4	1 9	3 5	.6	.4
Venous thromboses	16	12	17 1	13 0	6	6	6.9	5.8	7.3	6.3	1.8	2.3
Total extracardiac complications	53	54	57 2	57 8	23	24	22.7	26 0	24.5	27.8	7.0	9.3
Total, all thromboembolic complications	84	88	90.8	94 1	41	36	36.0	42.3	38.9	45.2	12.5	13.9

[a] Cases of unknown age are excluded from this tabulation but none developed any complications.
[b] For method of correction, see Appendix B.
[c] See footnote b of Table 96 of the text
[d] See footnote c of Table 96 of the text.

APPENDIX TABLE 42

NUMBER OF COMPLICATIONS, BY AGE: Total Number of Thromboembolic Complication Developing in the Control and Treated Groups during the Six-Week Period of Observation and Average Number of Such Complications per Hundred Cases, by Age and Status of Anticoagulant Therapy at Time Complication Developed

Age Group	Total Cases Observed		Number of Thromboembolic Complications												
			Total Number						Average Number per 100 Cases						
			Control Group		Treated Group				Control Group		Treated Group				
						Complications Occurring—						Complications Occurring—			
	Control Group	Treated Group	Total as reported for Six-Week Period[a]	Total Corrected for Exceptions in Treatment[b]	Total during Six-Week Period	While [illegible]	During [illegible]	After [illegible]	Total as re- [illegible]	Total Corrected [illegible]	Total during [illegible]	While Patient Not under Anticoagulant Therapy[c]	During First Three Days of Anticoagulant Therapy	Af Th Day Anti agul Th apy	
Under 40	9	17	5	5.4	2	1	—	1	—	—	*11.8*	*5.9*	—	*5*	
40–49	72	94	18	21.9	11	3	3	5	25.0	30.4	11.7	3.2	3.2	5	
50–59	152	218	61	63.5	28	12	2	14	40.1	41.8	12.8	5.5	.9	6	
60–69	133	172	57	61.5	21	5	4	12	42.9	46.2	12.2	2.9	2.3	7.	
70–79	70	72	30	31.5	13	5	1	7	42.9	45.0	18.1	7.0	1.4	9	
80–89	6	14	1	1.1	2	1	—	1	—	—	*14.3*	*7.1*	—	*7.*	
Age unknown	1	2	—	—	—	—	—	—	—	—	—	—	—	—	
All ages	442	589	172	184.9	77	27	10	40	38.9	41.8	13.1	4.6	1.7	6.	

Note: *Italics are used when rates quoted have less than 30 cases as a base since chance factors render su rates particularly unstable.*

[a] Control group counts include a total of 10 complications developing during anticoagulant therap Of these, 2 developed during the first 3 days of such therapy; 7, between the fourth and last day therapy; and 1, after the termination of therapy but while the prothrombin time was still elevate

[b] For explanation of method of correction, see Appendix B.

[c] Category includes complications developing prior to anticoagulant therapy, complications occu ring in cases not receiving anticoagulants because of contraindications, 1 complication occurring duri a prolonged break in therapy when the prothrombin time was probably normal, and 1 complicati developing after the termination of therapy when the prothrombin time had returned to normal.

[d] Defined to include all thromboembolic complications occurring from the fourth day of anticoag lant therapy through the day of the last dose and thereafter until the prothrombin time had return to 17 seconds or less, converted (or to 58% or more prothrombin activity). When no data were giv on prothrombin times subsequent to the day of the last dose, as very frequently happened, times we

APPENDIX TABLE 45

SEVERITY AT ONSET IN RELATION TO COMPLICATIONS, BY AGE: Number and Percentage of Cases Developing One or More Thromboembolic Complications, Number of Such Complications, and Average Number per Hundred Cases Developing in the Control and Treated Groups during the Six-Week Period of Observation, by Age and Severity of Illness at Onset

Age and Severity of Illness at Onset	Total Cases Observed		Cases Developing One or More Thromboembolic Complications				Number of Thromboembolic Complications					
			Number of Cases		Percentage of Cases		Total Number			Average Number per 100 Cases		
							Control Group			Control Group		
	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	[illegible]	Corrected [illegible]	Treated [illegible]	[illegible]	Corrected [illegible]	Treated Group
Mild or moderate at onset:												
Under 40	4	12	1	—	—[b]	*0.0*	3	3.2	—	—[b]	—[b]	*0.0*
40-49	57	68	12	4	21.1	5.9	14	17.0	4	24.6	29.8	5.9
50-59	109	154	21	12	19.3	7.8	29	30.2	12	26.6	27.7	7.8
60-69	101	116	21	13	20.8	11.2	37	39.9	14	36.6	39.5	12.1
70-79	*51*	*50*	16	4	31.4	8.0	18	18.9	5	35.3	37.1	10.0
80-89	3	6	1	1	—[b]	—[b]	1	1.1	1	—[b]	—[b]	—[b]
Age unknown	1	2	—	—	—[b]	—[b]	—	—	—	—[b]	—[b]	—[b]
Total mild or moderate[c]	326	408	72	34	22.1	8.3	102	110.3	36	31.3	33.8	8.8
Severe at onset:												
Under 40	5	5	1	2	—[b]	—[b]	2	2.2	2	—[b]	—[b]	—[b]
40-49	15	26	4	6	*26.7*	*23.1*	4	4.9	7	*26.7*	*32.7*	*26.9*
50-59	43	64	21	10	48.8	15.6	32	33.3	16	74.4	77.4	25.0
60-69	32	56	11	5	34.4	8.9	20	21.6	7	62.5	67.5	12.5
70-79	19	22	6	6	*31.6*	*27.3*	12	12.6	8	*63.2*	*66.3*	*36.4*
80-89	2	8	—	1	—[b]	—[b]	—	—	1	—[b]	—[b]	—[b]
Total severe[c]	116	181	43	30	37.1	16.6	70	74.6	41	60.3	64.3	22.7
All cases[c]	442	589	115	64	26.0	10.9	172	184.9	77	38.9	41.8	13.1

Note: *Italics are used when percentages and averages quoted have less than 30 cases as a base since chance factors render such figures particularly unstable.*

[a] For method of correction, see Appendix B

[b] Not computed since there were fewer than 10 cases in the sample.

[c] Rates not standardized for age. For rates standardized for age, see Table 102 of the text

APPENDIX TABLE 44

COMPLICATIONS, BY AGE AND SEX: Number and Percentage of Cases Developing One or More Thromboembolic Complications, Number of Such Complications, and Average Number per Hundred Cases Developing in the Control and Treated Groups during the Six-Week Period of Observation, by Age and Sex

Age and Sex	Total Cases Observed		Cases Developing One or More Thromboembolic Complications				Number of Thromboembolic Complications					
			Number of Cases		Percentage of Cases		Total Number			Average Number per 100 Cases		
							Control Group			Control Group		
	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
Males:												
Under 40	9	16	2	2	—[b]	*12 5*	5	5 4	2	—[b]	—[b]	*12.5*
40–49	63	82	15	10	23.8	12 2	17	20.8	*11*	*27.0*	*33.0*	13.4
50–59	121	189	35	20	28.2	10.6	51	53 1	25	41.1	42.8	13.2
60–69	97	109	26	10	26.8	9 2	43	46.4	13	44.3	47.8	11.9
70–79	48	42	15	3	31.3	7.1	22	23.1	3	45.8	48.1	7.1
80–89	4	5	1	2	—[b]	—[b]	1	1.1	2	—[b]	—[b]	—[b]
Age unknown	1	—	—	—	—[b]	—	—	—	—	—[b]	—[b]	—
Total males[c]	346	443	94	47	27.2	10.6	139	149.9	56	40.2	43.1	12.6
Females:												
Under 40	—	1	—	—	—	—[b]	—	—	—	—	—	—[b]
40–49	9	12	1	—	—[b]	*0 0*	1	1.1	—	—[b]	—[b]	*0 0*
50–59	28	29	7	2	*25.0*	*6.9*	10	10.4	3	*35.7*	*37.1*	*10 3*
60–69	36	63	6	8	16.7	12 7	14	15 1	8	38 9	41.9	12 7
70–79	22	30	7	7	*31.8*	23 3	8	8 4	*10*	*36.4*	*38.2*	33.3
80–89	1	9	—	—	—[b]	—[b]	—	—	—	—[b]	—[b]	—[b]
Age unknown	—	2	—	—	—	—[b]	—	—	—	—	—	—[b]
Total females[c]	96	146	21	17	21.9	11.6	33	35.0	21	34.4	36.5	*14.4*
All cases[c]	442	589	115	64	26.0	10.9	172	184 9	77	38 9	41.8	13.1

Note: *Italics are used when percentages and averages quoted have less than 50 cases as a base since chance factors render such figures particularly unstable.*

[a] For method of correction, see Appendix B.

[b] Not computed since there were fewer than 10 cases in the sample

[c] Rates not standardized for age. For rates standardized for age, see Table 101 of the text

APPENDIX TABLE 45

SEVERITY AT ONS... ge
of Cases Developin...
and Average Nu...
during the S... ...ge and Severity of Illness at Onset

Age and Severity of Illness at Onset	Total Cases Observed		Cases Developing One or More Thromboembolic Complications				Number of Thromboembolic Complications					
			Number of Cases		Percentage of Cases		Total Number			Average Number per 100 Cases		
							Control Group			Control Group		
	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
Mild or moderate at onset[c]												
Under 40	4	12	1	—	—[b]	*0.0*	3	3.2	—	—[b]	—[b]	0.0
40-49	57	68	12	4	21.1	5.9	14	17.0	4	24.6	29 8	5.9
50-59	109	154	21	12	19.3	7.8	29	30.2	12	26.6	27.7	7.8
60-69	101	118	21	13	20 8	11.2	37	39 9	14	36 6	30.5	12.1
70-79	51	50	16	4	31 4	8.0	18	18.9	5	35.3	37.1	10.0
80-89	3	6	1	1	—[b]	—[b]	1	1 1	1	—[b]	—[b]	—[b]
Age unknown	1	2	—	—	—[b]	—[b]	—	—	—	—[b]	—[b]	—[b]
Total mild or moderate[c]	326	408	72	34	22 1	8 3	102	110.3	36	31.3	33.8	8.8
Severe at onset												
Under 40	5	5	1	2	—[b]	—[b]	2	2 2	2	—[b]	—[b]	—[b]
40-49	15	26	4	6	*26 7*	*23 1*	4	4 9	7	*26.7*	*32.7*	*26.9*
50-59	43	64	21	10	48 8	15 6	32	33 3	16	74.4	77.4	25.0
60-69	32	56	11	5	34.4	8 9	20	21 6	7	62.5	67.5	12 5
70-79	19	22	6	6	*31.6*	*27 3*	12	12 6	8	*63.2*	*66 3*	*36.4*
80-89	2	8	—	1	—[b]	—[b]	—	—	1	—[b]	—[b]	—[b]
Total severe[c]	116	181	43	30	37.1	16.6	70	74 6	41	60 3	64.3	22 7
All cases[c]	442	589	115	64	26.0	10.9	172	184 9	77	38.9	41.8	13.1

Italics are used when percentages and averages quoted have less than 30 cases as a base since chance factors render such figures particularly unstable.

[a] For method of correction, see Appendix B

[b] Not computed since there were fewer than 10 cases in the sample.

[c] Rates not standardized for age. For rates standardized for age, see Table 102 of the text

APPENDIX TABLE 46

COMPLICATIONS IN GOOD AND POOR RISK CASES: Number of Cases Developing One or More Thromboembolic Complications and Number of Complications of Various Types in the Control and Treated Groups among Patients Estimated to Have Been Good and Poor Risk Cases by Criteria Approximating Those of Russek *et al.*[209]

Estimate of Risk	Total Cases *Observed*		Number of Cases Developing One or More *Thrombo-embolic* Complications		Number of Thromboembolic Complications[a]											
					All Types			Intracardiac Complications			Emboli[c, d]			Venous Thromboses		
					Control Group			Control Group			Control Group			Control Group		
	Control Group	Treated Group	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group
Moderately strict definition of good risk[e]*:*																
Good risk cases	65	114	15	10	18	18.6	10	10	10.3	9	6	6.2	—	2	2.1	1
Poor risk cases	377	475	100	54	154	166.3	67	55	59.6	21	73	78.7	35	26	28.0	11
Very strict definition of good risk[f]*:*																
Good risk cases	24	47	5	5	8	8.3	5	2	2.1	5	5	5.2	—	1	1.0	—
Poor risk cases	418	542	110	59	164	176.6	72	63	67.8	25	74	79.7	35	27	29.1	12

[a] Average number of complications per hundred cases, corrected for exceptions in treatment, are given in Table 103 of the text. Corresponding figures, not corrected for exceptions in treatment, may readily be computed from the above figures.

[b] For method of correction, see Appendix B

[c] Number of cases developing emboli in the control group for the good and poor risk categories in sequence were: 5 and 55 for the moderately strict definition and 4 and 56, for the very strict definition. Corresponding numbers of cases for the treated group were: zero and 30 for both definitions. One control group case in the poor risk category developing an arterial thrombosis has been excluded from the foregoing counts.

[d] See footnote c, Table 103 of the text.

[e] See definition on p. 231

[f] Same definition as for moderately strict except that third degree pain was added to the criteria for poor risk.

APPENDIX TABLE 47

[illegible]

Six-Week Period of Observation, by Age and Weight Status

Age and Weight Status[a]	Total Cases Observed		Cases Developing One or More Thromboembolic Complications				Number of Thromboembolic Complications					
			Number of Cases		Percentage of Cases		Total Number			Average Number per 100 Cases		
							Control Group			Control Group		
	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group
Cases 10% or more overweight												
Under 40	—	3	—	1	—	—[c]	—	—	1	—	—	—[c]
40-49	12	19	2	4	16.7	*21.1*	2	2.4	5	*16.7*	*20.0*	*26.3*
50-59	27	38	11	6	*40.7*	15.8	11	11.5	7	*40.7*	*42.6*	18.4
60-69	21	26	8	4	*38.1*	*15.4*	18	19.4	5	*85.7*	*92.4*	*19.2*
70-79	7	4	1	1	—[c]	—[c]	1	1.1	1	—[c]	—[c]	—[c]
80-89	1	—	—	—	—[c]	—	—	—	—	—[c]	—[c]	—
Total 10% or more overweight[d]	68	90	22	16	32.3	17.8	32	34.4	19	47.1	50.6	21.1
Cases within 10% of average weight:												
Under 40	2	8	—	—	—[c]	—[c]	—	—	—	—[c]	—[c]	—[c]
40-49	29	37	6	2	*20.7*	5.4	7	8.5	2	*24.1*	*29.3*	5.4
50-59	56	90	10	10	17.9	11.1	20	20.8	10	35.7	37.1	11.1
60-69	57	70	9	6	15.8	8.6	15	16.2	7	26.3	28.4	10.0
70-79	19	31	6	5	*31.6*	16.1	10	10.5	6	*52.6*	*55.3*	19.4
80-89	1	3	—	—	—[c]	—[c]	—	—	—	—[c]	—[c]	—[c]
Total within 10% of average weight[d]	164	239	31	23	18.9	9.6	52	56.0	25	31.7	34.1	10.5
Cases 10% or more underweight.												
Under 40	2	2	—	—	—[c]	—[c]	—	—	—	—[c]	—[c]	—[c]
40-49	4	6	1	—	—[c]	—[c]	1	1.2	—	—[c]	—[c]	—[c]
50-59	17	34	4	3	*23.5*	8.8	6	6.2	6	*35.3*	*36.5*	17.6
60-69	17	27	4	1	*23.5*	*3.7*	5	5.4	1	*29.4*	*31.8*	*3.7*
70-79	20	11	5	1	*25.0*	*9.1*	7	7.4	1	*35.0*	*37.0*	*9.1*
80-89	1	4	—	2	—[c]	—[c]	—	—	2	—[c]	—[c]	—[c]
Total 10% or more underweight[d]	61	84	14	7	23.0	8.3	19	20.2	10	31.1	33.1	11.9
Cases with weight unknown	149	176	48	18	32.2	10.2	69	74.3	23	46.3	49.9	13.1
All cases[d]	442	589	115	64	26.0	10.9	172	184.9	77	38.9	41.8	13.1

Note *Italics are used when percentages and rates quoted are based on less than 30 cases since chance factors render such figures particularly unstable*

[a] For method of classification of weight status, see footnote a, Table 11 of the text.

[b] For method of correction, see Appendix B

[c] Not computed since there were fewe[illegible]

[d] Rates not standardized for age For [illegible]

APPENDIX TABLE 46

COMPLICATIONS IN GOOD AND POOR RISK CASES: Number of Cases Developing One or More Thromboembolic Complications and Number of Complications of Various Types in the Control and Treated Groups among Patients Estimated to Have Been Good and Poor Risk Cases by Criteria Approximating Those of Russek *et al.*[209]

Estimate of Risk	Total Cases Observed		Number of Cases Developing One or More Thromboembolic Complications		Number of Thromboembolic Complications[a]											
					All Types			Intracardiac Complications			Emboli[c,d]			Venous Thromboses		
					Control Group			Control Group			Control Group			Control Group		
	Control Group	Treated Group	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group
Moderately strict definition of good risk[e]:																
Good risk cases	65	114	15	10	18	18.6	10	10	10 3	9	6	6.2	—	2	2.1	1
Poor risk cases	377	475	100	54	154	166.3	67	55	59 6	21	73	78.7	35	26	28.0	11
Very strict definition of good risk[f]:																
Good risk cases	24	47	5	5	8	8.3	5	2	2.1	5	5	5.2	—	1	1.0	—
Poor risk cases	418	542	110	59	164	176.6	72	63	67.8	25	74	79.7	35	27	29.1	12

[a] Average number of complications per hundred cases, corrected for exceptions in treatment, are given in Table 103 of the text Corresponding figures, not corrected for exceptions in treatment, may readily be computed from the above figures.

[b] For method of correction, see Appendix B.

[c] Number of cases developing emboli in the control group for the good and poor risk categories in sequence were: 5 and 55 for the moderately strict definition and 4 and 56, for the very strict definition Corresponding numbers of cases for the treated group were: zero and 30 for both definitions One control group case in the poor risk category developing an arterial thrombosis has been excluded from the foregoing counts.

[d] See footnote *c*, Table 103 of the text.

[e] See definition on p 231

[f] Same definition as for moderately strict except that third degree pain was added to the criteria for poor risk.

COMPLICATIONS, BY TYPE, IN RELATION TO LOCATION OF ORIGINAL INFARCTION: Number and Type of Thromboembolic Complications Developing in the Control and Treated Groups and Average Number of Such Complications per Hundred Cases among Patients Whose Original Infarctions Were in Various Locations

Type and Location of Complication	Control Group						Treated Group		
	Anterior Infarction at Onset[a] (231 Cases)		Posterior Infarction at Onset[a] (171 Cases)		All Other Types[a] (40 Cases)		Anterior [illegible]	Posterior [illegible]	[illegible]
	As Reported	Corrected for Exceptions in Treatment[b]	As Reported	Corrected for Exceptions in Treatment[b]	[illegible]	[illegible] ment[b]			
	Number of Thromboembolic Complications								
Secondary myocardial infarctions:									
Extensions	25	26.9	12	12 0	3	3.2	10	7	2
New infarctions	9	9.6	14	15.1	2	2.2	5	5	1
Total intracardiac complications	34	36.5	26	28.0	5	5 4	15	12	3
Emboli:									
Pulmonary	24	25.8	21	22.5	3	3.2	14	9	5
Cerebral[c]	12	13 0	8	8 6	—	—	3	1	—
Peripheral and visceral[d]	6	6.4	4	4 3	1	1.1	2	1	—
Venous thromboses	11	11.8	14	15 1	3	3 2	4	4	4
Total extracardiac complications	53	57.0	47	50 5	7	7.5	23	15	9
Total, all thromboembolic complications	87	93.5	73	78 5	12	12 9	38	27	12
	Average Number of Thromboembolic Complications per 100 Cases								
Secondary myocardial infarctions									
Extensions	10.8	11.6	7.0	7.6	7.5	8.0	3.1	3.3	3.4
New infarctions	3.9	4 2	8.2	8.8	5.0	5.5	1.6	2.4	1.7
Total intracardiac complications	14 7	15 8	15 2	16 4	12 5	13.5	4.7	5.7	5.1
Emboli:									
Pulmonary	10.4	11.2	12.3	13 2	7 5	8.0	4.4	4.2	8.5
Cerebral[c]	5 2	5 6	4.7	5.0	—	—	9	.5	—
Peripheral and visceral[d]	2.6	2.8	2 3	2.5	2.5	2.8	6	.5	—
Venous thromboses	4.8	5 1	8.2	8 8	7.5	8.0	1.3	1.9	6.8
Total extracardiac complications	23 0	24 7	27.5	29 5	17.5	18 8	7.2	7.1	15.3
Total, all thromboembolic complications	37.7	40.5	42.7	45 9	30.0	32.3	11.9	12.8	20.4

[a] For definition of locations, see footnotes b, c, and d of Table 106 of the text.
[b] For method of correction, see Appendix B.
[c] See footnote b, Table 96 of the text.
[d] See footnote c, Table 96 of the text.

APPENDIX TABLE 48

CASES DEVELOPING COMPLICATIONS IN RELATION TO TYPE OF HOSPITAL SERVICE

Number and Percentage of Cases Developing One or More Thromboembolic Complications among Cases Receiving Various Types of Hospital Service, by Age and Status of Anticoagulant Therapy at Time of First Complication

Age Group and Type of Hospital Service	Number of Cases		Cases Developing One or More Thromboembolic Complications									
			Number of Cases					Percentage of Cases				
				Treated Group					Treated Group			
					First Complication Occurring—					First Complication Occurring—		
	Control Group	Treated Group	Control Group—Total during Six-Week Period[a]	Total during Six-Week Period	While Patient Not under Anticoagulant Therapy[b]	During First Three Days of Anticoagulant Therapy	After Third Day of Anticoagulant Therapy[c]	Control Group—Total during Six-Week Period[a]	Total during Six-Week Period	While Patient Not under Anticoagulant Therapy[b]	During First Three Days of Anticoagulant Therapy	After Third Day of Anticoagulant Therapy[c]
Private or semiprivate service:												
Under 50	31	36	6	3	1	—	2	19.4	8.3	2.8	—	5.5
50–59	52	84	14	10	4	1	5	26.9	11.9	4.8	1.2	5.9
60–69	46	68	12	2	—	—	2	26.1	2.9	—	—	2 9
70 and over	26	33	8	7	3	—	4	*30.8*	21.2	9.1	—	12.1
Total private or semiprivate service[d]	155[e]	221[e]	40	22	8	1	13	25.8	10 0	3.6	.5	5 9
Ward service:												
Under 50	49	67	12	7	1	2	4	24.5	10.4	1.5	3.0	5 9
50–59	98	127	28	12	5	1	6	28 6	9.4	3.9	.8	4.7
60–69	86	96	20	16	4	2	10	23 3	16.7	4.2	2.1	10.4
70 and over	47	51	14	5	1	1	3	29.8	9.8	2.0	2 0	5 8
Age unknown	1	2	—	—	—	—	—	—[f]	—[f]	—[f]	—[f]	—[f]
Total ward service[d].	281[e]	343[e]	74	40	11	6	23	26.3	11.7	3.2	1.8	6.7
Mixed types of service.	6	25	1	2	2	—	—	—[f]	*8.0*	*8.0*	—	—
All cases	442	589	115	64	21	7	36	26.0	10.9	3.6	1.2	6.1

Note: *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such rates particularly unstable.*

[a] See footnote a, Appendix Table 41.

[b] See footnote b, Appendix Table 41

[c] See footnote c, Appendix Table 41.

[d] Rates not standardized for age. For standardized rates, see Table 105 of the text. [illegible] although

[e] This figure differs from [illegible] ses re- indicating that five to ten [illegible] ases in ceived private and which, [illegible] this table. They are all tabulated in the private or semiprivate category.

[f] Not computed since there were fewer than 10 cases in the sample.

APPENDIX TABLE 51

COMPLICATIONS IN RELATION TO INITIAL CONGESTIVE HEART FAILURE AND INITIAL SHOCK, BY PERIOD OF ILLNESS *Number of Thromboembolic Complications Developing in the Control and Treated Groups during the First Week and from the Second through the Sixth Week of the Illness among Patients Who Showed or Did Not Show Initial Congestive Heart Failure and/or Initial Shock*

Status of Initial Congestive Heart Failure and Initial Shock[a]	Number of Cases: Beginning Study: Control Group	Number of Cases: Beginning Study: Treated Group	Number of Cases: Surviving to Beginning of Second Week: Control Group	Number of Cases: Surviving to Beginning of Second Week: Treated Group	Total Number: Control Group: As Reported: All Weeks	Total Number: Control Group: As Reported: In 1st Week	Total Number: Control Group: As Reported: In 2nd-6th Week	Total Number: Control Group: Corrected for Exceptions in Treatment[b]: All Weeks	Total Number: Control Group: Corrected for Exceptions in Treatment[b]: In 1st Week	Total Number: Control Group: Corrected for Exceptions in Treatment[b]: In 2nd-6th Week	Total Number: Treated Group: All Weeks	Total Number: Treated Group: In 1st Week	Total Number: Treated Group: In 2nd-6th Week	Average Number per 100 Cases[c]: Control Group: As Reported: All Weeks	Average Number per 100 Cases[c]: Control Group: As Reported: In 1st Week	Average Number per 100 Cases[c]: Control Group: As Reported: In 2nd-6th Week	Average Number per 100 Cases[c]: Control Group: Corrected for Exceptions in Treatment[b]: All Weeks	Average Number per 100 Cases[c]: Control Group: Corrected for Exceptions in Treatment[b]: In 1st Week	Average Number per 100 Cases[c]: Control Group: Corrected for Exceptions in Treatment[b]: In 2nd-6th Week[d]	Average Number per 100 Cases[c]: Treated Group: All Weeks	Average Number per 100 Cases[c]: Treated Group: In 1st Week	Average Number per 100 Cases[c]: Treated Group: In 2nd-6th Week
Initial heart failure but no initial shock	76	75	68	60	20	5	15	21 3	5 1	16 2	10*	3	6	26.3	0 6	22.1	28.0	6.7	23.0	13.3	4.0	8.7
Initial shock but no initial heart failure	54	83	50	75	20	9	11	22 1	9.3	12 8	5	1	4	37 0	16 7	22.0	40.9	17.2	25.7	6.0	1.2	5 3
Both initial heart failure and initial shock	31	37	23	27	10	3	7	10 5	3.1	7.4	7	3	4	32 3	9.7	*30.4*	33.9	10.0	*32.7*	18.0	8.1	*14.8*
All cases with initial heart failure[f]	107	112	91	96	30	8	22	31 8	8 2	23 6	17*	6	10	28 0	7 5	21.2	29 7	7.7	26.1	15.2	5.4	10.4
All cases with initial shock[g]	85	120	73	102	30	12	18	32 6	12 4	20 2	12	4	8	35 3	14 1	21.7	38.1	14.6	27.9	10.0	3.3	7.8
All cases with either initial heart failure or initial shock[h]	161	195	141	171	50	17	33	53 9	17.5	36.4	22*	7	14	31.1	10.6	23.4	33.5	10.9	25.9	11.3	3.6	8.2
Neither initial heart failure nor initial shock . .	281	394	209	378	122*	28	92	131.0*	28.7	100.1	55*	10	40	43.4	10.0	31.2	40.6	10.2	37.3	14.0	2.5	10.6
All cases . .	442	589	410	549	172*	45	125	184.9*	46.2	136.5	77*	17	54	38.9	10.2	30.5	41.8	10.5	33.4	13.1	2.9	9.8

footnotes to table 51 on next page

APPENDIX TABLE 50

COMPLICATIONS IN RELATION TO ABNORMAL RHYTHMS: Number and Percentage of Cases Developing One or More Thromboembolic Complications, Number of Such Complications and Average Number per Hundred Cases Developing in the Control and Treated Groups during the Six-Week Period of Observation among Patients Showing Various Types of Abnormal Rhythms during the First Week of Their Illness

Type of Abnormal Rhythm	Number of Cases		Cases Developing One or More Thromboembolic Complications				Number of Thromboembolic Complications					
			Number of Cases		Percentage of Cases		Total Number			Average Number per 100 Cases		
							Control Group			Control Group		
	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
Specific types of abnormal rhythms:[b]												
Auricular fibrillation	30	39	9	8	30.0	20.5	13	14.0	10	43.3	46.7	25.6
Heart block of any type or degree	43	60	11	8	25.6	13.3	15	16.1	10	34.9	37.4	16.7
Left or right bundle branch block	20	47	5	7	*25.0*	14.9	5	5.4	8	*25.0*	*27.0*	17.0
Premature contractions, ectopic beats or extrasystoles[c]	64	82	16	9	25.0	11.0	19	20.4	10	29.7	31.9	12.2
Any type of abnormal rhythm[d]	162	204	46	25	28.4	12.3	66	71.0	29	40.7	43.8	14.2
No abnormal rhythm	271	378	66	39	24.4	10.3	102	109.6	48	37.6	40.4	12.7
Total cases with status of abnormal rhythms known	433	582	112	64	25.9	11.0	168	180.6	77	38.8	41.7	13.2
All cases	442	589	115	64	26.0	10.9	172	184.9	77	38.9	41.8	13.1

Note: *Italics are used when percentages and averages quoted are based on less than 50 cases since chance factors render such figures particularly unstable*

[a] For method of correction, see Appendix B.

[b] Types of rhythms other than those listed were found in too small numbers to form an adequate basis for rates.

[c] Represents unduplicated totals for persons with these general types of abnormal rhythms. For number of cases showing specific rhythms within these categories, see Appendix Table 16

[d] Represents unduplicated total for cases with any abnormal rhythm (Some cases showed two or more types of abnormal rhythms.) For definition of abnormalities included, see footnote e, Table 107 of the text.

APPENDIX TABLE 51

COMPLICATIONS IN RELATION TO INITIAL CONGESTIVE HEART FAILURE AND INITIAL SHOCK, BY PERIOD OF ILLNESS: Number of Thromboembolic Complications Developing in the Control and Treated Groups during the First Week and from the Second through the Sixth Week of the Illness among Patients Who Showed or Did Not Show Initial Congestive Heart Failure and/or Initial Shock

Status of Initial Congestive Heart Failure and Initial Shock[a]	Number of Cases				Number of Thromboembolic Complications																	
					Total Number									Average Number per 100 Cases[a]								
	Beginning Study		Surviving to Beginning of Second Week		Control Group						Treated Group			Control Group						Treated Group		
					As Reported			Corrected for Exceptions in Treatment[b]						As Reported			Corrected for Exceptions in Treatment[b]					
	Control Group	Treated Group	Control Group	Treated Group	All Weeks	In 1st Week	In 2nd-6th Week	All Weeks	In 1st Week	In 2nd-6th Week	All Weeks	In 1st Week	In 2nd-6th Week	All Weeks	In 1st Week	In 2nd-6th Week	All Weeks	In 1st Week	In 2nd-6th Week[d]	All Weeks	In 1st Week	In 2nd-6th Week
Initial heart failure but no initial shock	76	75	68	69	20	5	15	21.3	5.1	10.2	10[e]	3	6	20.3	6.6	22.1	28.0	6.7	23.9	13.3	4.0	8.7
Initial shock but no initial heart failure	54	83	50	75	20	9	11	22.1	0.3	12.8	5	1	4	37.0	16.7	22.0	40.9	17.2	25.7	0.0	1.2	5.3
Both initial heart failure and initial shock	31	37	23	27	10	3	7	10.5	3.1	7.4	7	3	4	32.3	9.7	*30.4*	33.9	10.0	*32.7*	18.9	8.1	*14.8*
All cases with initial heart failure[f]	107	112	91	96	30	8	22	31.8	8.2	23.6	17[e]	6	10	28.0	7.5	21.2	29.7	7.7	26.1	15.2	5.4	10.4
All cases with initial shock[g]	85	120	73	102	30	12	18	32.6	12.4	20.2	12	4	8	35.3	14.1	24.7	38.4	14.6	27.9	10.0	3.3	7.8
All cases with either initial heart failure or initial shock[h]	161	195	141	171	50	17	33	53.9	17.5	30.4	22[e]	7	14	31.1	10.6	23.4	33.5	10.9	25.9	11.3	3.6	8.2
Neither initial heart failure nor initial shock	281	394	269	378	122[e]	28	92	131.0[e]	28.7	100.1	55[e]	10	40	43.4	10.0	31.2	46.6	10.2	37.3	14.0	2.5	10.6
All cases . . .	442	589	410	549	172[e]	45	125	184.9[e]	46.2	136.5	77[e]	17	54	38.9	10.2	30.5	41.8	10.5	33.4	13.1	2.9	9.8

footnotes to table 51 on next page

footnotes to table 51. Note: *Italics are used when rates quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] For definitions, see footnote a, Table 103 of the text.

[b] For method of correction, see Appendix B.

[c] Rates for the first week and all weeks are based on the total number of cases in each group beginning the study. Rates for the second through the sixth week are based on the number of cases (corrected and uncorrected) beginning the second week. Consequently, the rates for the component periods cannot be added to secure the total for all weeks.

[d] Rates in this column are based on the number of survivors at the beginning of the second week corrected for exceptions in treatment. These counts are not shown since they differ very little from counts in Column 3. They may be computed by deducting deaths in the first week, corrected for exceptions in treatment, from number of cases at the beginning of the study. (Categories totalled 409 instead of 410.)

[e] Totals for all weeks include complications for which the week of occurrence was unknown; hence they exceed total of counts for first week and later weeks. Contrary to Appendix Table 40, 3 control group complications and 1 treated group complication of known period but unknown day are here reported in appropriate subgroups. Two control and 6 treated group complications could not be so allocated and hence are omitted in the details by weeks although not from the totals.

[f] Totals of lines 1 and 3.

[g] Totals of lines 2 and 3.

[h] Totals of lines 1, 2, and 3.

APPENDIX TABLE 52

COMPLICATIONS IN RELATION TO CONGESTIVE HEART FAILURE AND SHOCK AFTER THE FIRST WEEK: Number of Thromboembolic Complications Developing in the Control and Treated Groups during the Second through the Sixth Week of the Illness and Average Number per Hundred Cases Surviving at the Beginning of the Second Week and Showing or Not Showing Congestive Heart Failure and/or Shock after the First Week

Status of Congestive Heart Failure[a] and Shock after the First Week	Total Cases Surviving to Beginning of Second Week[b]		Number of Thromboembolic Complications Developing after the First Week					
			Total Number			Average Number per 100 Survivors at Beginning of Second Week		
	Control Group	Treated Group	Control Group		Treated Group	Control Group		Treated Group
			As Reported	Corrected for Exceptions in Treatment[c]		As Reported	Corrected for Exceptions in Treatment[c, d]	
Heart failure but no shock	75	85	34	36.5	14	45 3	48.9	16.5
Shock but no heart failure	10	7	5	5.6	1	*50.0*	*56.0*	—[e]
Both heart failure and shock	13	12	6	6.8	6[f]	*46.2*	*52 3*	*50.0*[f]
All cases with heart failure[g]	88	97	40	43 3	20	45.5	49.4	20.6
All cases with shock[h]	23	19	11	12.4	7	*47.8*	*53.9*	*36.8*
All cases with either heart failure or shock[i]	98	104	45	48 9	21	45.9	50.1	20.2
Neither heart failure nor shock	312	445	80	87.6	33	25 6	28.1	7 4
All cases	410	549	125[j]	136 5	54[j]	30.5	33.4	9.8

Note: *Italics are used when rates quoted are based on less than 50 cases since chance factors render such figures particularly unstable*

[a] See footnote a, Table 109 of the text.

[b] See footnote b, Table 109 of the text

[c] For method of correction, see Appendix B.

[d] See footnote d, Appendix Table 51

[e] Not computed since there were fewer than 10 cases in the sample.

[f] Three (or half) of these complications occurred before the beginning of anticoagulants in one case where therapy was delayed because of a history of gastric ulcer with hematemesis.

[g] Totals of lines 1 and 3

[h] Totals of lines 2 and 3.

[i] Totals of lines 1, 2, and 3.

[j] Includes 2 complications in the control group and 1 complication in the treated group excluded from Appendix Table 40 since period only and not week of occurrence was known Complications of unknown date are omitted

APPENDIX TABLE 53

TYPES OF BLEEDING: Number of Episodes of Bleeding of Various Types in the Control and Treated Groups and Relation of Episodes to Anticoagulant Therapy

Type of Bleeding	Number of Episodes of Bleeding			
	Control Group[a] (442 Cases)	Treated Group (589 Cases)		
		Total Episodes	Episodes Probably Unrelated to Anticoagulant Therapy[b]	Episodes Probably Due to, or Aggravated by, Anticoagulant Therapy
Hematuria, total	6	41	13	28
Microscopic	6	31	11	20
Gross	—	10	2	8
Hemoptysis	11	15	12	3
Hematemesis and/or melena	8	10	9	10
Epistaxis	—	9	1	8
Other types	1	6	1	5
All episodes	26	90	36	54

[a] Excludes 5 episodes of bleeding believed due to, or aggravated by, anticoagulants given to certain control patients after the development of thromboembolic complications. One episode where the role of anticoagulants is completely unknown is not excluded.

[b] Includes 2 episodes where the role of anticoagulants is completely unknown.

APPENDIX TABLE 54

SEVERITY OF BLEEDING EPISODES: Number and Percentage of Episodes of Bleeding of Various Degrees of Severity in the Control and Treated Groups and Relation of Episodes to Anticoagulant Therapy

Severity of Episode	Episodes of Bleeding							
	Control Group[a] (442 Cases)	Treated Group (589 Cases)						
		Total Episodes	Episodes Probably Unrelated to Anticoagulant Therapy			Episodes Probably Related to Anticoagulant Therapy		
			Total Episodes	Those Beginning When Patient Not under Anticoagulant Therapy	Those Beginning during Anticoagulant Therapy[b] but Probably Not Due to This Therapy[c]	Total Episodes	Those Probably Due to Anticoagulant Therapy	Those Probably Aggravated by Anticoagulant Therapy
	Number of Episodes							
Mild	18	52	23	8	15	29	22	7
Moderate	8	32	11	6	5	21	15	6
Severe	—	5	1	1	—	4	1	3
Severity unknown	—	1	1	1	—	—	—	—
Total episodes	26	90	36	16	20	54	38	16
	Percentage of Episodes							
Mild	*69*	58	64	*50*	*75*	54	58	*44*
Moderate	*31*	36	30	*38*	*25*	39	39	*37*
Severe	—	5	3	*6*	—	7	3	*19*
Severity unknown	—	1	3	*6*	—	—	—	—
Total episodes	100	100	100	100	100	100	100	100

Note: *Italics are used when percentage distributions quoted have less than 30 cases as a base since chance factors render such distributions particularly unstable.*

[a] Counts exclude 5 episodes of bleeding believed related to anticoagulants in patients receiving anticoagulants ... where the ...

APPENDIX TABLE 55

BLEEDING EPISODES ON A DAY-RATE BASIS, BY SEVERITY: Average Number of Mild, Moderate, and Severe Bleeding Episodes Related and Unrelated to Anticoagulants per Thousand Days of Illness Observed with and without Anticoagulant Therapy in the Control and Treated Groups

Severity of Episode	Average Number of Bleeding Episodes per 1000 Days of Given Type of Therapy Observed[a]							
		Treated Group						
			Episodes Probably Unrelated to Anticoagulant Therapy			Episodes Probably Related to Anticoagulant Therapy (Number per 1000 Days of Anticoagulant Therapy)		
	Control Group[b] (Number [illegible]	Total Episodes [illegible]	[illegible]	[illegible]	[illegible]	Total Episodes	Those Probably Due to Anticoagulant Therapy	Those Probably Aggravated by Anticoagulant Therapy
Mild	1.1	2 4	1 1	1 4	.9	1 8	1.4	.4
Moderate	5	1.5	.5	1 0	.3	1.3	.9	.4
Severe . .	—	2	—[e]	.2	—	.2	—[e]	.2
Severity unknown	—	—[e]	—[e]	2	—	—	—	—
Total episodes	1 6	4 1	1 6	2.8	1.2	3.3	2.3	1.0
	Number of Days							
Total days of given type of therapy observed	15,769	21,854	21,854	5,646	16,208	16,208	16,208	16,208

[a] For number of episodes reported, see Appendix Table 54.

[b] Control group rates exclude 5 episodes of bleeding due to, or aggravated by, anticoagulants but include 1 episode occurring under anticoagulant therapy where the role of anticoagulants is completely unknown

[c] See footnote b, Appendix Table 54

[d] See footnote c, Appendix Table 54

[e] Less than 05 episodes per 1000 days

APPENDIX TABLE 56

BLEEDING EPISODES, BY WEEK OF ILLNESS: Total Number of Bleeding Episodes and Average Number Related and Unrelated to Anticoagulants per Thousand Days of Illness Observed with and without Anticoagulant Therapy in the Control and Treated Groups, by Week of Illness When Episode Began

Week of Illness and Treatment Group	Number of Survivors from Previous Week	Number of Days of Illness Observed			Number of Bleeding Episodes			Average Number of Bleeding Episodes per 1000 Days of Given Type of Therapy Observed		
		Total Days	Days without Anticoagulant Therapy	Days with Anticoagulant Therapy[a]	Total Episodes	Episodes Probably Unrelated to Anticoagulant Therapy	Episodes Probably Due to, or Aggravated by, Anticoagulant Therapy	Total Episodes (Number per 1000 Days of Illness Observed)	Episodes Probably Unrelated to Anticoagulant Therapy (Number per 1000 Days of Illness Observed)	Episodes Probably Due to, or Aggravated by, Anticoagulant Therapy (Number per 1000 Days of Anticoagulant Therapy)
Control group:										
First week	442	3,023	2,985	38	15	14	1	5.0	4.6	26.3
Second week	410	2,759	2,661	98	9	8	1	3.3	2.9	10.2
Third week	378	2,595	2,457	138	1	—	1	.4	0.0	7.2
Fourth week	365	2,506	2,345	161	2	1	1	.8	.4	6.2
Fifth week	351	2,452	2,286	166	2	1	1	8	4	6.0
Sixth week	349	2,434	2,280	154	1	1	—	.4	.4	0 0
Total period	442	15,769	15,014	755	31[b, c]	26[b]	5[c]	2.0[c]	1.6	6.6[c]
Treated group:										
First week	589	4,038	1,702	2,336	27	20	7	6 7	5.0	3 0
Second week	549	3,738	315	3,423	22	6	16	5.9	1.6	4.7
Third week	518	3,588	175	3,413	11	2	9	3.1	.6	2.6
Fourth week	508	3,525	342	3,183	9	1	8	2.5	.3	2.5
Fifth week	500	3,493	979	2,514	11	2	9	3.1	.6	3.6
Sixth week	497	3,472	2,133	1,339	8	3	5	2 3	.9	3.7
Total period	589	21,854	5,646	16,208	90[d]	36[d]	54	4.1	1.6	3 3

[a] For definition of days under therapy, see Appendix Table 58, footnote a.

[b] Totals include one episode for which the week of occurrence was not reported.

[c] See footnote c of Appendix Table 58.

[d] Totals include two episodes for which the week of occurrence was not reported.

APPENDIX TABLE 57

[BL]EEDING, BY AGE: Number and Percentage of Cases Bleeding with and without Relation to Anticoagulant Therapy in the Control and Treated Groups, Number of Bleeding Episodes Related and Unrelated to Anticoagulant Therapy, and Number per Hundred Cases, by Age

Age Group	Number of Cases		Cases Having One or More Episodes of Bleeding								Episodes of Bleeding							
			Control Group[a]		Treated Group						Control Group[a]		Treated Group					
					Total Cases Bleeding (Unduplicated)[b]		Cases Having One or More Episodes Probably Unrelated to Anticoagulant Therapy		Cases Having One or More Episodes of Bleeding Probably Due to, or Aggravated by, Anticoagulant Therapy				Total Episodes		Episodes Probably Unrelated to Anticoagulant Therapy[d]		Episodes Probably Due to, or Aggravated by, Anticoagulant Therapy	
	Control Group	Treated Group	Number	Per Cent of Cases	Number	Per Cent of Cases	Number	Per Cent of Cases	Number	Per Cent of Cases	Number	Number per 100 Cases	Number	Number per 100 Cases	Number	Number per 100 Cases	Number	Number per 100 Cases
Under 50	81	111	2	2.5	12	10.8	5	4 5	8	7.2	3	3.7	15	13 5	5	4.5	10	9.0
50-59	152	218	9	5.9	33	15.1	16	7 3	20	9.2	10	6.6	41	18.8	16	7.3	25	11.5
60-69	133	172	9	6.8	21	12.2	7	4.1	14	8 1	9	6 8	22	12.8	7	4.1	15	8.7
70 and over	75	86	3	4 0	9	10 5	6	7 0	4	4.7	4	5 3	11	12 8	7	8.1	4	4.7
Age unknown	1	2	—	—[e]	1	—[e]	1	—[e]	—	—[e]	—	—[e]	1	—[e]	1	—[e]	—	—[e]
All ages	442	589	23	5.2	76	12.9	35	5.9	46	7.8	26	5.9	90	15.3	36	6.1	54	9.2

[a] Counts represent the number of cases bleeding due to causes unrelated to anticoagulants or to unknown causes

[b] Cases having 1 or more episodes of bleeding unrelated to anticoagulants and other episodes related to anticoagulants are not counted twice in th...

[c] Excludes 5 episo... control patients afte... anticoagulants is cor... ...not excluded

[d] Includes 2 episodes of bleeding where the role of anticoagulants is completely unknown.

[e] Percentages and rates not recorded since there were fewer than 10 cases in the group

APPENDIX TABLE 56

BLEEDING EPISODES, BY WEEK OF ILLNESS: Total Number of Bleeding Episodes and Average Number Related and Unrelated to Anticoagulants per Thousand Days of Illness Observed with and without Anticoagulant Therapy in the Control and Treated Groups, by Week of Illness When Episode Began

Week of Illness and Treatment Group	Number of Survivors from Previous Week	Number of Days of Illness Observed			Number of Bleeding Episodes			Average Number of Bleeding Episodes per 1000 Days of Given Type of Therapy Observed		
		Total Days	Days without Anticoagulant Therapy	Days with Anticoagulant Therapy[a]	Total Episodes	[illegible]	Episodes [illegible]	Total [illegible]	Episodes Probably [illegible] Observed)	Episodes Probably Due to, or [illegible] agulant Therapy)
Control group:										
First week...	442	3,023	2,985	38	15	14	1	5.0	4.6	26.3
Second week..	410	2,759	2,661	98	9	8	1	3.3	2.9	10.2
Third week	378	2,595	2,457	138	1	—	1	.4	0.0	7.2
Fourth week	365	2,506	2,345	161	2	1	1	.8	.4	6.2
Fifth week..	351	2,452	2,286	166	2	1	1	.8	.4	6.0
Sixth week ...	349	2,434	2,280	154	1	1	—	.4	.4	0.0
Total period	442	15,769	15,014	755	31[b, c]	26[b]	5[c]	2.0[c]	1.6	6.6[c]
Treated group:										
First week	589	4,038	1,702	2,336	27	20	7	6.7	5.0	3.0
Second week ..	549	3,738	315	3,423	22	6	16	5.9	1.6	4.7
Third week.	518	3,588	175	3,413	11	2	9	3.1	.6	2.6
Fourth week	508	3,525	342	3,183	9	1	8	2.5	.3	2.5
Fifth week	500	3,493	979	2,514	11	2	9	3.1	.6	3.6
Sixth week .	497	3,472	2,133	1,339	8	3	5	2.3	.9	3.7
Total period	589	21,854	5,646	16,208	90[d]	36[d]	54	4.1	1.6	3.3

[a] [illegible] see Appendix Table 58, footnote a.

[d] Totals include two episodes for which the week of occurrence was not reported.

APPENDIX TABLE 59

BLEEDING DURING DICUMAROL THERAPY IN RELATION TO SELECTED PATHOLOGICAL CONDITIONS Number of Cases Developing Bleeding Related and Unrelated to Dicumarol during Dicumarol Therapy among All Cases Receiving Dicumarol and Having a Known Degree of Reaction to Dicumarol, by Presence or Absence of Selected Pathological Conditions during the Illness

Status of Bleeding and Its Relation to Dicumarol	Number of Cases Bleeding during Dicumarol Therapy[a] among Cases with and without Selected Pathological Conditions during the Illness[b]					
	Azotemia and/or Renal Disease		Liver Enlargement		Congestive Failure	
	Present	Not Present	Present	Not Present	Present	Not Present
Cases developing bleeding related to dicumarol	11	34	9	36	13	32
Cases developing bleeding unrelated to dicumarol	5	14	5	14	9	10
Total cases developing bleeding of any type[c]	15	47	14	48	22	40
	Number of Cases in Group					
Total cases in total sample receiving dicumarol and having known degree of reaction to dicumarol[a]	48	490	64	474	121	417

[a] For specifications as to cases included in this tabulation, see footnote a, Table 116 of the text.
[b] For specifications, see footnote b, Table 116 of the text.
[c] Two cases had 1 episode related and 1 episode unrelated to dicumarol. Hence combined subgroups sometimes exceed the total.

APPENDIX TABLE 60

DAYS OF HEPARIN THERAPY: Number of Days and Percentage of Total Days of Anticoagulant Therapy on Which Patients in the Total Sample and in the Control and Treated Groups Received Heparin

Treatment Group and Status of Anticoagulant Therapy	Days of Anticoagulant Therapy				Percentage of Total Days of Anticoagulant Therapy When Heparin Was Given
	Total Days of Anticoagulant Therapy	Days When Patient Received Heparin[a]			
		Total Days of Heparin	Heparin Only	Heparin Plus Dicumarol[b]	
Days during first three days of anticoagulant therapy					
Control group	106	54	10	44	50.9
Treated group	1,712	179	24	155	10.5
Total sample	1,818	233	34	199	12.8
Days between fourth day and day of last dose					
Control group	611	9	3	6	1.5
Treated group	12,986	27	16	11	.2
Total sample	13,597	36	19	17	.3

[a] For exclusions, see footnote b, Table 3 of the text.
[b] Days on which patient was under *the* influence of dicumarol were counted here even though patient did *not* receive a dose of dicumarol on that particular day.

APPENDIX TABLE 58

BLEEDING EPISODES ON A DAY-RATE BASIS, BY AGE: Total Number of Bleeding Episodes and Average Number Related and Unrelated to Anticoagulants per Thousand Days of Illness Observed with and without Anticoagulant Therapy in the Control and Treated Groups, by Age

Age and Treatment Group	Number of Cases	Number of Days of Illness Observed			Number of Bleeding Episodes			Average Number of Bleeding Episodes per 1000 Days of Given Type of Therapy Observed		
		Total Days	Days [illegible]	Days [illegible]	[illegible]	Episodes Probably [illegible]	Episodes Probably Due to [illegible] Therapy	Total Episodes (Number per 1000 Days of Illness Observed)	Episodes Probably Unrelated to Anticoagulant Therapy (Number per 1000 Days of Illness Observed)	Episodes Probably Due to, or Aggravated by, Anticoagulant Therapy (Number per 1000 Days of Anticoagulant Therapy)
Control group:										
Under 50	81	3,131	2,993	138	5	3	2	1.6	1.0	—[b]
50-59	152	5,902	5,614	288	13	10	3	2.2	1.7	10.4
60-69	133	4,466	4,171	295	9	9	—	2.0	2 0	0 0
70 and over	75	2,228	2,194	34	4	4	—	1.8	1.8	—[b]
Age unknown	1	42	42	—	—	—	—	—[b]	—[b]	—[b]
All ages. . .	442	15,769	15,014	755	31[c]	26	5[c]	2.0[c]	1.6	6.6[c]
Treated group:										
Under 50	111	4,401	1,266	3,135	15	5	10	3 4	1 1	3.2
50-59	218	8,419	2,063	6,356	41	16	25	4 9	1.9	3 9
60-69	172	6,159	1,603	4,556	22	7	15	3.6	1.1	3.3
70 and over	86	2,791	708	2,083	11	7	4	3 9	2.5	1.9
Age unknown	2	84	6	78	1	1	—	—[b]	—[b]	—[b]
All ages . .	589	21,854	5,646	16,208	90	36	54	4.1	1.6	3.3

[a] Includes all days under heparin plus all days between the first and last dose of dicumarol and thereafter until the prothrombin time returned to 17 seconds (58%), or if no times were reported after the last dose, through the fourth day thereafter.

[b] *Not reported because of the small number of patients represented by the observed days.*

[c] These figures do not agree with those cited in tables on bleeding not computed on a day basis since such tables omit 5 episodes in the control group believed due to, or aggravated by, anticoagulants.

APPENDIX TABLE 62

DEATHS, BY WEEK OF ILLNESS: Number of Cases Dying and Having or Not Having One or More Thromboembolic Complications during the Illness among Survivors in the Control and Treated Groups at the Beginning of Each Week, by Week of Illness

Week of Illness	Number of Survivors from Previous Week			Number of Deaths[b]								
				All Cases Dying			Cases Dying—No Thromboembolic Complications			Cases Dying—One or More Thromboembolic Complications		
	Control Group			Control Group			Control Group			Control Group		
	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
First week	442	442.0	589	32	33.0	40	26	26.0	35	6	7.0	5
Second week	410	409.0	549	32	34.3	31	17	17.0	26	15	17.3	5
Third week	378	374.7	518	13	14.4	10	7	7.0	6	6	7.4	4
Fourth week	365	360.3	508	14	15.9	8	7	7.0	4	7	8.9	4
Fifth week	351	344.4	500	2	2.4	3	2	2.0	1	—	.4	2
Sixth week	349	342.0	497	3	3.5	2	1	1.0	—	2	2.5	2

[a] For method of correction, see Appendix B

[b] Percentage of cases dying for the control group, corrected for exceptions in treatment, and for the treated group are given in Table 126 of the text. Corresponding percentages for the control group, not corrected for exceptions in treatment, can be readily computed from the figures given above.

APPENDIX TABLE 63

DEATHS, BY AGE Number of Cases Dying in the Control and Treated Groups and Having or Not Having One or More Thromboembolic Complications during the Illness, by Age

Age Group	Total Cases Observed		Number of Cases[a]								
			All Cases Dying			Cases Dying—No Thromboembolic Complications			Cases Dying—One or More Thromboembolic Complications		
			Control Group			Control Group			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group
Under 40	9	17	2	2.0	1	2	2.0	1	—	—	—
40-49	72	94	8	8.3	8	6	6.0	4	2	2.3	4
50-59	152	218	18	18.4	24	9	9.0	18	9	9.4	6
60-69	133	172	38	43.1	34	23	23.0	28	15	20.1	6
70-79	70	72	28	29.5	19	19	19.0	15	9	10.5	4
80-89	5	14	2	2.2	8	1	1.0	6	1	1.2	2
Age unknown	1	2	—	—	—	—	—	—	—	—	—
All ages	442	589	96	103.5	94	60	60.0	72	36	43.5	22

[a] Percentage of cases dying in the control group, corrected for exceptions in treatment [illegible] treated group are given in Tables 123 and 127 of the [illegible] for exceptions in [illegible] rate and the tre[illegible] were fewer than [illegible]

[b] For methoc[illegible] ppendix B.

APPENDIX TABLE 61

CASES DEVELOPING THROMBOEMBOLIC COMPLICATIONS UNDER OR FOLLOWING HEPARIN: *Number and Percentage of Cases in the Treated Group Receiving Heparin Sometime during the First Three Days Who Developed Thromboembolic Complications during the First Three Days or from the Fourth through the Sixth Day*[a]

Type of Anticoagulant Received during First Three Days of Anticoagulant Therapy	First Three Days of Anticoagulant Therapy			Fourth through Sixth Day of Anticoagulant Therapy, or First Three Days after Termination of Heparin When Heparin Was Continued beyond Three Days		
	Number of Cases Beginning Period	Number of Cases Developing Complications	Per Cent of Cases Developing Complications	Number of Cases Beginning Period[b]	Number of Cases Developing Complications	Per Cent of Cases Developing Complications
Treated group cases[c] *receiving during the first three days of anticoagulant therapy:*						
Some combination of heparin and dicumarol	88[d]	1[e]	1.1[e]	79	—	0.0
Heparin only	5	—	—[f]	3	—[g]	—[f, g]
Dicumarol only	484	8[h]	1.7[i]	454	4	.9
Total treated group cases receiving anticoagulants	577	9	1.6	530	4	.8

[a] Since it was important to learn whether a compensating increase in complications occurred after the termination of heparin, the first three days following the termination of heparin were tabulated instead of the fourth to the sixth day inclusive in cases where heparin was continued beyond three days.

[b] Case counts in this section omit cases dying before the fourth day of therapy and cases in which anticoagulants were discontinued prior to the fourth day (or the first day after the termination of heparin).

[c] See footnote a, Table 122 of the text.

[d] [illegible] the first day, 59 received [illegible] other 12 cases received only [illegible] nticoagulants on later days.

[e] [illegible] arin was discontinued after the second day; thus it did not occur on a day [illegible]

[f] Not computed since there were fewer than 10 cases in the sample.

[g] In one case receiving heparin on the fourth day, a complication occurred on that day. It is not [illegible] definition (see footnote a, this table).

[h] [illegible] complications on the second day of anticoagulants. Thus the [illegible] the first three days among patients receiving dicumarol only was nine.

[i] The average number of complications per 100 cases during the first three days among patients receiving dicumarol only was 1.9.

APPENDIX TABLE 65

DEATHS IN RELATION TO WEIGHT STATUS: Number and Percentage of Cases Dying in the Control and Treated Groups, by Weight Status in Relation to Normal and Age

Weight Status in Relation to Normal and Age Group	Total Cases Observed		Number of Cases Dying			Percentage of Cases Dying		
			Control Group			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
10% or more overweight:								
Under 40	—	3	—	—	—	—	—	—[b]
40-49	12	19	1	1.0	1	*8.3*	*8.3*	*5.3*
50-59	27	38	5	5.1	5	*18.5*	*18.9*	13.2
60-69	21	26	10	11.3	5	*47.6*	*53.8*	*19.2*
70-79	7	4	1	1.1	1	—[b]	—[b]	—[b]
80-89	1	—	—	—	—	—[b]	—[b]	—
Total 10% or more overweight[c]	68	90	17	18.5	12	25.0	27.2	13.3
Within 10% of normal weight:								
Under 40	2	8	—	—	1	—[b]	—[b]	—[b]
40-49	29	37	1	1.0	3	*3.4*	*3.4*	8.1
50-59	56	90	3	3.0	9	5.4	5.4	10.0
60-69	57	70	13	14.8	8	22.8	26.0	11.4
70-79	19	31	6	6.3	9	*31.6*	*33.2*	29.0
80-89	1	3	—	—	1	—[b]	—[b]	—[b]
Total within 10% of normal weight[c]	164	230	23	25.1	31	14.0	15.3	13.0
10% or more underweight:								
Under 40	2	2	—	—	—	—[b]	—[b]	—[b]
40-49	4	6	—	—	—	—[b]	—[b]	—[b]
50-59	17	34	3	3.1	3	*17.6*	*18.2*	8.8
60-69	17	27	1	1.1	5	*5.9*	*6.5*	*18.5*
70-79	20	11	10	10.5	3	*50.0*	*52.5*	*27.3*
80-89	1	4	—	—	3	—[b]	—[b]	—[b]
Total 10% or more underweight[c]	61	84	14	14.7	14	22.9	24.1	16.7
Weight status unknown	149	176	42	45.2	37	28.2	30.3	21.0
All cases	442	589	96	103.5	94	21.7	23.4	16.0

Note: *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] For method of correction, see Appendix B.

[b] Not computed since there were fewer than 10 cases in the sample.

[c] Rates not standardized for age. For standardized rates, see Table 129 of the text.

APPENDIX TABLE 64

DEATHS, BY SEX: Number and Percentage of Cases Dying in the Control and Treated Groups, by Sex and Age

Sex and Age	*Total Cases Observed*		Number of Cases Dying			Percentage of Cases Dying		
			Control Group			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
Males:								
Under 50	72	98	7	7.2	8	9.7	10.0	8.2
50–59	124	169	16	16.4	19	12.9	13.2	10.1
60–69	97	109	25	28.4	21	25.7	29.3	19.3
70 and over	52	47	21	22.2	17	40.4	42.7	36.2
Age unknown	1	—	—	—	—	—[b]	—[b]	—
Total males[c]	346	443	69	74.2	65	19.9	21.4	14.7
Females:								
Under 50	9	13	3	3.1	1	—[b]	—[b]	7.7
50–59	28	29	2	2.0	5	7.1	7.1	17.2
60–69	36	63	13	14.7	13	36.1	40.8	20.6
70 and over	23	39	9	9.5	10	39.1	41.3	25.6
Age unknown	—	2	—	—	—	—	—	—[b]
Total females[c]	96	146	27	29.3	29	28.1	30.5	19.9
All cases	442	589	96	103.5	94	21.7	23.4	16.0

Note: *Italics are used when percentages quoted are based on less than 50 cases since chance factors render such figures particularly unstable.*

[a] For method of correction, see Appendix B.

[b] Not computed since there were fewer than 10 cases in the sample.

[c] Rates not standardized for age. For standardized rates, see Table 128 of the text.

APPENDIX TABLE 67

DEATHS IN RELATION TO A POSITIVE OR NEGATIVE MEDICAL HISTORY OF VARIOUS CONDITIONS. Number of Cases Dying in the Control and Treated Groups among Patients with a Positive or Negative Medical History of Various Conditions, by Age for Selected Conditions

Condition in Medical History	Total Cases Observed[a]				Number of Cases Dying[b]			
	Present		Absent		Present		Absent	
	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group
Coronary artery disease:								
Anginal syndrome	223	285	205	285	45	44	47	45
One or more previous infarctions.								
Under 50 . .	17	19	61	89	2	4	8	5
50–59 .	35	45	106	155	5	10	12	10
60–69 .	29	38	93	121	7	6	27	25
70 and over .	18	21	52	60	5	9	22	16
Age unknown	—	—	1	2	—	—	—	—
All ages .	99	123	313	427	19	29	69	56
Clinical evidence of previous coronary disease.								
Under 50	41	55	37	48	5	7	5	2
50–59	101	121	43	86	12	14	5	8
60–69	85	105	38	48	24	21	11	7
70 and over	42	51	21	27	12	14	10	11
Age unknown	—	2	—	—	—	—	—	—
All ages	269	334	139	209	53	59	31	28
Other cardiac history								
Congestive heart failure	66	82	364	489	21	27	70	58
Other heart disease	44	67	360	462	10	15	69	57
Cardiovascular and other conditions:								
Arteriosclerosis	209	246	192	300	55	54	29	27
Hypertension	148	221	229	295	36	42	38	34
Diabetes	51	62	384	517	15	11	77	79

[a] See footnote a, Table 131 of the text

[b] Percentage of cases dying (corrected for exceptions in treatment) including age-standardized rates for the categories "one or more previous infarctions" and "clinical evidence of previous coronary disease" can be found in Table 131 of the text Percentage of cases dying, not corrected for exceptions in treatment, can readily b- are as actually reported Correctior actual number of deaths without r corrected for exceptions in treatme in computing the percentage dying in various categories in Table 131 of the text, increase the number of deaths as given above in each category by 7.8 per cent.

APPENDIX TABLE 66

DEATHS, BY TYPE OF SERVICE: Number and Percentage of Cases Dying in the Control and Treated Groups among Patients Receiving Private or Semiprivate Care and among Patients Receiving Ward Care, by Age

Type of Service and Age Group	Total Cases Observed		Number of Cases Dying			Percentage of Cases Dying		
			Control Group			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
Private or semiprivate:								
Under 50	31	36	3	3.1	4	*9.7*	*10.0*	11.1
50-59	52	84	6	6.1	7	11.5	11.7	8.3
60-69	46	68	11	12.5	8	23.9	27.2	11.8
70 and over	26	33	9	9.5	6	*34.6*	*36.5*	18.2
Total private or semiprivate[b]	*155*[c]	*221*[c]	*29*	*31.2*	25	18.7	20.1	11.3
Ward:								
Under 50	49	67	7	7.2	4	14.3	14.7	6.0
50-59	98	127	12	12.3	17	12.2	12.6	13.4
60-69	86	96	27	30.6	24	31.4	35.6	25 0
70 and over	47	51	21	22.2	20	44 7	47.2	*39 2*
Age unknown	1	2	—	—	—[d]	—[d]	—[d]	—[d]
Total ward[b]	281[c]	343[c]	67	72 3	65	23.8	25.7	19.0
Mixed types	*6*	*25*	—	—	4	—[d]	—[d]	*16.0*
All cases	442	589	96	103 5	94	21.7	23.4	16 0

Note: *Italics are used when percentages quoted are based on less than 50 cases since chance factors render such figures particularly unstable.*

[a] For method of correction, see Appendix B

[b] Rates not standardized for age For standardized rates, see Table 130 of the text.

[c] This figure differs from the corresponding one in Appendix Table 33 since Michael Reese Hospital, although indicating that 5 to 10 per cent of their cases received ward care, did not identify which cases received private and which, ward care. Since it was impossible to allocate specific Michael Reese cases to the correct private and ward categories, these cases are all considered private cases in this table.

[d] Not computed since there were fewer than 10 cases in the sample.

APPENDIX TABLE 69

DEATHS IN RELATION TO PRESENCE OR ABSENCE OF THROMBOEMBOLIC COMPLICATIONS. Number and Percentage of Cases Dying in the Control and Treated Groups among Patients Developing One or More Thromboembolic Complications and among Patients Developing No Thromboembolic Complications during the Six-Week Period of the Illness, by Age

Status of Thromboembolic Complications during the Illness and Age	Total Cases Observed		Number of Cases Dying			Percentage of Cases Dying		
			Control Group			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
No thromboembolic complications:								
Under 40	7	14	2	2.0	1	—[b]	—[b]	*7.1*
40–49	56	85	6	6.0	4	10.7	10.7	4.7
50–59	110	196	9	9.0	18	8.2	8.2	9.2
60–69	101	154	23	23.0	28	22.8	22.8	18.2
70–79	48	62	19	19.0	15	39.6	39.6	24.2
80–89	4	12	1	1.0	6	—[b]	—[b]	*50.0*
Age unknown	1	2	—	—	—	—[b]	—[b]	—[b]
Total, no thromboembolic complications[c]	327	525	60	60.0	72	18.3	18.3	13.7
One or more thromboembolic complications:								
Under 40	2	3	—	—	—	—[b]	—[b]	—[b]
40–49	16	9	2	2.3	4	*12.5*	*14.4*	—[b]
50–59	42	22	9	9.4	6	21.4	22.4	*27.3*
60–69	32	18	15	20.1	6	46.9	62.8	*33.3*
70–79	22	10	9	10.7	4	*40.9*	*48.6*	*40.0*
80–89	1	2	1	1.0	2	—[b]	—[b]	—[b]
Total, one or more thromboembolic complications[c]	115	64	36	43.5	22	31.3	37.8	34.4
All cases	442	589	96	103.5	94	21.7	23.4	16.0

Note: *Italics are used when percentages quoted are based on less than 50 cases since chance factors render such figures particularly unstable.*

[a] For method of correction, see Appendix B.

[b] Not computed since there were fewer than 10 cases in the sample.

[c] Rates not standardized for age. For standardized rates, see Table 134 of the text.

APPENDIX TABLE 68

DEATHS, BY SEVERITY OF ILLNESS AT ONSET: Number and Percentage of Cases Dying in the Control and Treated Groups, by Severity of Illness at Onset and Age

Severity of Illness at Onset and Age Group	Total Cases Observed		Number of Cases Dying			Percentage of Cases Dying		
			Control Group			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
Mild or moderate at onset:								
Under 40	4	12	—	—	—	—[b]	—[b]	*0.0*
40–49	*57*	*68*	*2*	*2.1*	*2*	*3.5*	*3.7*	2.9
50–59	109	154	9	9.2	*7*	8.3	8.4	4.5
60–69	101	116	18	20.4	9	17.8	20.2	7.8
70–79	*51*	*50*	*13*	*13.7*	*8*	*25.5*	*26.9*	*16.0*
80–89	3	6	1	1.1	2	—[b]	—[b]	—[b]
Age unknown	1	2	—	—	—	—[b]	—[b]	—[b]
Total mild or moderate[c]	326	408	43	46.5	28	13.2	14.3	6.9
Severe at onset:								
Under 40	*5*	*5*	2	2.0	1	—[b]	—[b]	—[b]
40–49	*15*	*26*	*6*	*6.2*	6	*40.0*	*41.3*	*23.1*
50–59	43	64	9	9.2	*17*	20.9	21.4	26.6
60–69	32	56	20	22.7	25	62.5	70.9	44.6
70–79	*19*	*22*	*15*	*15.8*	*11*	*78.9*	*83.2*	*50.0*
80–89	2	8	1	1.1	6	—[b]	—[b]	—[b]
Total severe[c]	*116*	*181*	*53*	*57.0*	*66*	*45.7*	*49.1*	36.5
All cases	442	589	96	103.5	94	21.7	23.4	16.0

Note: *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] *For method of correction, see Appendix B.*

[b] Not computed since there were fewer than 10 cases in the sample.

[c] Rates not standardized for age. For standardized rates, see Table 132 of the text

APPENDIX TABLE 71

DEATHS IN RELATION TO ABNORMAL RHYTHMS: Number of Cases Dying in the Control and Treated Groups among Patients Who Showed Various Types of Abnormal Rhythms during the First Week of the Illness

Type of Abnormal Rhythm	Total Cases Observed		Number of Cases Dying[a]		
			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[b]	Treated Group
Specific types of abnormal rhythms:[c]					
Auricular fibrillation	30	39	10	12.8	11
Heart block, any type or degree	43	60	16	17.3	21
Left or right bundle branch block	20	47	5	5.4	15
Premature contractions, ectopic beats, or extrasystoles	64	82	14	15.1	17
Any type of abnormal rhythm[d]	162	204	50	53.9	51
No abnormal rhythm	271	378	43	46.4	40
Total cases with status of abnormal rhythms known	433	582	93	100.3	91
All cases	442	589	96	103.5	94

[a] Percentage of cases dying in the control group corrected for exceptions in treatment is given in Tabl... ... , not corrected for exceptions in treatment, can readily

APPENDIX TABLE 70

DEATHS IN RELATION TO LOCATION OF ORIGINAL INFARCTION: Number of Cases Dying in the Control and Treated Groups among Patients Whose Original Infarctions Were in Various Locations, by Age

Location of Original Infarction and Age Group	Total Cases Observed		Number of Cases Dying			Percentage of Cases Dying		
			Control Group			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group	As Reported	Corrected for Exceptions in Treatment[a]	Treated Group
Cases with single original infarction:								
Anterior, anterolateral, or anteroseptal:								
Under 50	45	64	6	6.2	7	13.3	13.8	10.9
50–59	82	113	12	12.2	11	14.6	14.9	9.7
60–69	66	99	19	21.5	17	28.8	32.6	17.2
70 and over	37	42	14	14.9	14	*37.8*	*40.3*	*33.3*
Age unknown	1	1	—	—	—	—[b]	—[b]	—[b]
Total anterior[c]	231	319	51	54.8	49	22.1	23.7	15.4
Posterior, posterolateral, and posteroseptal:								
Under 50	30	39	3	3.1	1	*10.0*	10.3	2.6
50–59	63	82	5	5.1	9	7.9	8.1	11.0
60–69	52	59	15	17.0	10	28.8	32.7	16.9
70 and over	26	30	10	10.6	5	*38.5*	*40.8*	16.7
Age unknown	—	1	—	—	—	—	—	—[b]
Total posterior[c]	171	211	33	35.8	25	19.3	20.9	11.8
Septal	7	8	3	3.2	2	—[b]	—[b]	—[b]
Diffuse changes	25	25	7	7.5	8	*28.0*	*30.0*	*32.0*
Site obscure or unknown[d]	6	19	2	2.2	7	—[b]	—	*36.8*
Cases with two original *infarctions*[e]	2	7	—	—	3	—[b]	—[b]	—[b]
All cases	442	589	96	103.5	94	21.7	23.4	16.0

Note: *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such figures particularly unstable.*

[a] For method of correction, see Appendix B.

[b] Not computed since there were less than 10 cases in the sample

[c] [illegible] For standardized rates, see Table 135 of the text.

[d] [illegible] in 2 other cases the location [illegible] case, the classification of [illegible]

[e] In these cases, 2 infarctions apparently [illegible]aneously, or 2 major areas were involved in a single infarction. The following sites were found in various combinations: 4 anterior, 1 anteroseptal, 6 posterior, 1 posteroseptal, and 6 diffuse changes

APPENDIX TABLE 73

DEATHS IN RELATION TO CONGESTIVE HEART FAILURE AND SHOCK AFTER [illegible]

Status of Congestive Heart Failure[a] and Shock after the First Week	Total Cases Surviving to Beginning of Second Week[b]		Number of Cases Surviving to Beginning of Second Week Dying Second through Sixth Week[c]		
			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[d]	Treated Group
Heart failure but no shock	75	85	24	26.6	22
Shock but no heart failure	10	7	6	6.4	2
Both heart failure and shock	13	12	9	10.0	10
All cases with heart failure[e]	88	97	33	36.6	32
All cases with shock[f]	23	19	15	16.4	12
All cases with either heart failure or shock[g]	98	104	39	43.0	34
Neither heart failure nor shock	312	445	25	27.5	20
All cases	410	549	64	70.5	54

[a] See footnote a, Table 138 of the text.

[b] Counts for the number of survivors in the control group at the beginning of the second week corrected for exceptions in treatment are not shown. With this correction, categories totalled 409 instead of 410.

[c] Percentage of cases dying second to sixth week in the control group (corrected for exceptions in treatment) and in the treated group are given in Table 138 of the text. Percentage of cases dying in the control group, not corrected for exceptions in treatment, can readily be computed from the above figures.

[d] For method of correction, see Appendix B.

[e] Totals of lines 1 and 3.

[f] Totals of lines 2 and 3.

[g] Totals of lines 1, 2 and 3.

APPENDIX TABLE 72

DEATHS IN RELATION TO INITIAL CONGESTIVE HEART FAILURE AND SHOCK, BY PERIOD OF ILLNESS: Number and Percentage of Cases Dying in the Control and Treated Groups during the First Week and from the Second through the Sixth Week of the Illness among Patients Who Showed or Did Not Show Initial Heart Failure and/or Initial Shock

Status of Initial Congestive Heart Failure and Shock[a]	Total Cases Observed: Beginning Study: Control Group	Total Cases Observed: Beginning Study: Treated Group	Total Cases Observed: Surviving to Beginning of Second Week: Control Group	Total Cases Observed: Surviving to Beginning of Second Week: Treated Group	Number of Cases Dying: Control Group: As Reported: All Weeks	Number of Cases Dying: Control Group: As Reported: In 1st Week	Number of Cases Dying: Control Group: As Reported: In 2nd–6th Week	Number of Cases Dying: Control Group: Corrected for Exceptions in Treatment[b]: All Weeks	Number of Cases Dying: Control Group: Corrected for Exceptions in Treatment[b]: In 1st Week	Number of Cases Dying: Control Group: Corrected for Exceptions in Treatment[b]: In 2nd–6th Week	Number of Cases Dying: Treated Group: All Weeks	Number of Cases Dying: Treated Group: In 1st Week	Number of Cases Dying: Treated Group: In 2nd–6th Week	Percentage of Cases Dying[c]: Control Group: As Reported: All Weeks	Percentage of Cases Dying[c]: Control Group: As Reported: In 1st Week	Percentage of Cases Dying[c]: Control Group: As Reported: In 2nd–6th Week	Percentage of Cases Dying[c]: Control Group: Corrected for Exceptions in Treatment[b]: All Weeks	Percentage of Cases Dying[c]: Control Group: Corrected for Exceptions in Treatment[b]: In 1st Week	Percentage of Cases Dying[c]: Control Group: Corrected for Exceptions in Treatment[b]: In 2nd–6th Week[d]	Percentage of Cases Dying[c]: Treated Group: All Weeks	Percentage of Cases Dying[c]: Treated Group: In 1st Week	Percentage of Cases Dying[c]: Treated Group: In 2nd–6th Week
Initial heart failure but no initial shock	76	73	69	69	20	8	12	21.2	8.2	13.0	18	6	12	26.3	10.5	17.6	27.9	10.8	19.2	24.0	8.0	17.4
Initial shock but no initial heart failure	54	83	50	75	13	4	9	13.9	4.1	9.8	15	8	7	24.1	7.4	19.0	25.7	7.6	19.6	18.1	9.6	9.2
Both initial heart failure and initial shock	*31*	*37*	*23*	*27*	*11*	*8*	*3*	*11.9*	*8.4*	*3.5*	*16*	*10*	*6*	*35.5*	*25.8*	*13.0*	*38.4*	*27.1*	*15.5*	*43.2*	*27.0*	*22.2*
All cases with initial heart failure[e]	107	112	91	96	31	16	15	33.1	16.6	16.5	34	16	18	29.0	15.0	16.5	30.9	15.5	18.3	30.4	14.3	18.8
All cases with initial shock[f]	83	120	73	102	24	12	12	25.8	12.4	13.3	31	18	13	28.2	14.1	16.4	30.4	14.7	18.3	25.8	15.0	12.7
All cases with either initial heart failure or initial shock[g]	161	195	141	171	44	20	24	47.0	20.7	26.3	49	24	25	27.3	12.4	17.0	29.2	12.9	18.7	25.1	12.3	14.6
Neither initial heart failure nor initial shock	281	394	269	378	52	12	40	56.5	12.3	44.2	43	16	29	18.5	4.3	14.9	20.1	4.4	16.4	11.4	4.1	7.7
All cases	*442*	*539*	*410*	*549*	*96*	*32*	*64*	*103.5*	*33.0*	*70.5*	*94*	*40*	*54*	*21.7*	*7.2*	*15.6*	*23.4*	*7.5*	*17.2*	*16.0*	*6.8*	*9.8*

Note: *Italics are used when percentages quoted are based on less than 50 cases since chance factors render such figures particularly unstable*

[a] For definitions, see footnote a, Table 137 of the Text

[b] For method of correction, see Appendix B.

[c] Percentages for the first week and all weeks are based on the total number of cases in each group beginning the study. Percentages for the second through the sixth week are based on the number of cases beginning the second week. Consequently, the percentages for the component periods cannot be added to secure the total for all weeks

[d] Percentages in this column are based on the number of survivors at the beginning of the second week, corrected for exceptions in treatment, counts for which are not shown. They may be computed by deducting deaths in the first week, corrected for exceptions from number of cases at the beginning of the study

[e] Totals of lines 1 and 3.

[f] Totals of lines 2 and 3.

[g] *Totals of lines 1, 2, and 3*

APPENDIX TABLE 73

DEATHS IN RELATION TO CONGESTIVE HEART FAILURE AND SHOCK AFTER THE FIRST WEEK: Number of Cases Dying in the Control and Treated Groups during the Second through the Sixth Week of the Illness among Patients Who Survived to the Beginning of the Second Week and Showed Congestive Heart Failure and/or Shock, or Neither, after the First Week

Status of Congestive Heart Failure[a] and Shock after the First Week	Total Cases Surviving to Beginning of Second Week[b]		Number of Cases Surviving to Beginning of Second Week Dying Second through Sixth Week[c]		
			Control Group		
	Control Group	Treated Group	As Reported	Corrected for Exceptions in Treatment[d]	Treated Group
Heart failure but no shock	75	85	24	26.6	22
Shock but no heart failure	10	7	6	6.4	2
Both heart failure and shock	13	12	9	10.0	10
All cases with heart failure[e]	88	97	33	36.6	32
All cases with shock[f]	23	19	15	16.4	12
All cases with either heart failure or shock[g]	98	104	39	43.0	34
Neither heart failure nor shock	312	445	25	27.5	20
All cases	410	549	64	70.5	54

[a] See footnote a, Table 138 of the text.

[b] Counts for the number of survivors in the control group at the beginning of the second week corrected for exceptions in treatment are not shown. With this correction, categories totalled 409 instead of 410.

[c] Percentage of cases dying second to sixth week in the control group (corrected for exceptions in treatment) and in the treated group are given in Table 138 of the text. Percentage of cases dying in the control group, not corrected for exceptions in treatment, can readily be computed from the above figures.

[d] For method of correction, see Appendix B.

[e] Totals of lines 1 and 3.

[f] Totals of lines 2 and 3.

[g] Totals of lines 1, 2 and 3.

APPENDIX TABLE 74

HOSPITAL PROTHROMBIN TIME DILUTION CURVES FOR NORMAL BLOOD: Mean, Median, and Range of Prothrombin Times (in Seconds) Found for Ten Normal Blood Samples at Various Plasma Concentrations by Each Participating Hospital

Hospital[a]	Prothrombin Time (in seconds) at Various Plasma Concentrations[b]														
	100 Per Cent			50 Per Cent			25 Per Cent			12.5 Per Cent			6.25 Per Cent		
	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Bellevue, New York	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Beth Israel, Boston	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cincinnati General	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cleveland City	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Henry Ford, Detroit	13.7	14.0	11.8–14.8	15.7	15.8	13.5–17.8	20.5	20.0	16.8–24.8	30.4	29.3	25.0–40.0	50.8	51.4	40.5–56.3
Jackson Memorial, Miami	14.8	14.3	12.6–17.2	17.1	17.0	14.9–19.9	21.6	22.0	19.7–24.4	33.1	33.5	30.2–36.3	52.4	53.8	42.8–56.2
Lakeside, Cleveland	15.0	15.0	13.9–16.0	17.9	17.7	15.7–20.3	23.9	23.9	21.7–26.7	35.2	35.3	29.0–43.8	68.6	67.8	48.5–70.0
Massachusetts General, Boston	16.3	16.5	15.0–17.0	23.6	23.5	21.0–25.0	35.3	35.5	31.0–39.0	59.4	57.0	35.0–68.0	93.3[c]	93.5[c]	82.0–114.0[c]
Michael Reese, Chicago	13.0	13.2	12.1–13.6	15.5	15.7	14.0–16.6	21.1	21.5	18.4–22.8	34.8	34.2	29.8–41.3	65.9	63.6	51.4–92.1
Mount Zion and San Francisco, San Francisco:															
Rabbit brain thromboplastin	13.2	13.0	12.3–14.1	18.5	18.2	16.6–20.7	29.5	27.3	25.3–31.6	45.9	46.0	40.8–56.2	137.5[d]	130.2[d]	106.8–203.4[d]
Human brain thromboplastin	12.3	12.5	11.6–13.0	15.5	15.7	14.9–17.3	23.4	23.1	20.7–26.3	39.0	38.6	35.7–45.1	134.6[d]	137.9[d]	95.7–185.8[d]
The New York Hospital, New York	15.3	15.4	14.0–16.3	17.4	17.4	15.4–19.2	24.1	24.5	21.4–28.2	39.1	39.4	34.9–41.6	68.9	68.7	59.7–80.9
Pennsylvania, Philadelphia	13.5	13.0	12.5–16.0	16.4	16.5	14.0–18.0	21.1	21.3	17.5–23.5	30.2	31.0	24.5–35.5	49.7	52.0	39.5–59.0
Peter Bent Brigham, Boston	16.0	15.6	14.7–18.2	19.2	18.8	17.1–21.0	23.6	23.4	21.1–37.5	39.1	37.8	33.8–50.7	68.4	68.1	57.5–79.2
Rhode Island, Providence	18.0	18.0	13.0–21.0	22.3	21.5	19.0–28.5	32.7	32.3	24.0–40.0	58.3	52.8	41.0–92.5	114.4	102.5	63.0–155.0

[a] For methods and thromboplastins used by each hospital, see Appendix Table 75 and footnotes. The Veterans Administration Hospital, Bronx, New York did not report dilution curves for normal blood.

[b] All figures are based on 10 normal blood samples. Usually each sample was tested in duplicate and these duplicate tests were averaged and used in this form in all further computations. San Francisco and Mount Zion reported 4 readings per sample and Lakeside and Peter Bent Brigham only one. Samples were usually tested on different days under varying laboratory conditions. Most tests were run late in 1947.

[c] Based on only 4 readings since others had uncertain end points.

[d] Figures represent 5 per cent level since 6.25 per cent readings were not reported.

APPENDIX TABLE 75, PART 1

PROTHROMBIN TIME CONVERSION TABLE: Prothrombin Times for Each Participating Hospital Approximately Equivalent at Time of Study to Specific Intervals on Composite Dilution Curve Used as Standard in This Study and to Which Reported Prothrombin Times Were Converted for the Purpose of Increasing Interhospital Comparability

Prothrombin Time Interval on Composite Curve (Converted)[a]		Prothrombin Time Intervals for Individual Hospitals before Conversion (in seconds)[a]															
		Hospitals Using the Link-Shapiro Modification of the Quick Method (Comparable Thromboplastin)									Hospitals Using the Quick Method						
											Rabbit Brain Thromboplastin (Commercial)			Other Types of Thromboplastin[i]			
						Michael Reese								Massachusetts General			
In Seconds	In Per Cent Prothrombin Activity	Bellevue[b]	Cleveland City	Jackson Memorial	Lakeside, Cleveland	Curve 1[c]	Curve 2[d]	New York, N. Y.	Pennsylvania, Philadelphia[e]	Peter Bent Brigham[f,g]	Beth Israel	Cincinnati General	Henry Ford[f,h]	Curve 1[j]	Curve 2[k]	San Francisco and Mount Zion[l]	Rhode Island[f,g]
Under 15	Over 100%	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15
15-17	100-[illegible]																
18-19																	
20-22																	
23-24																	
25-29																	
30-34																	
35-39																	
40-49										[illegible]-41	50-59	30-34	33-37	53-58	63-70	44-52	41-44
50-59										—[m]	60-84	35-43	38-45	59-70	71-84	53-70	—[m]
60 and over										—[m]	85-111	44-53	47-54	71-80	85-96	71-90	—[m]
	under	51 and over	60 and over	54 and over	63 and over	78 and over	64 and over	68 and over	52 and over	—[m]	112 and over	54 and over	55 and over	81 and over	97 and over	91 and over	—[m]

[a] Actual reported times were rounded to nearest whole second before conversion. Converted equivalents were stated to nearest whole second after conversion. Except where otherwise stated, curves were developed by the method described on pp 350-352. Reported prothrombin times were based on the average of two or more determinations for all hospitals except the following: Cleveland City, Henry Ford, Jackson Memorial, Lakeside, Michael Reese, Mount Zion, Pennsylvania, and Rhode Island. Some of these hospitals routinely doing only single determinations did second determinations under special circumstances where indicated.

[b] Early Bellevue prothrombin times were determined at The New York Hospital. Times quoted apply to cases whose times were determined in Bellevue laboratories.

[c] Applicable to cases treated before July, 1947.

[d] Applicable to cases treated after June 30, 1947.

[e] Curve is that used in the conversion of Pennsylvania cases treated after August 1, 1947. Prothrombin procedures prior to this date were not sufficiently refined to justify conversion.

[f] Curve was developed from supplemental data furnished by the hospital applicable to specific control times since the use of the method described on pp 350-352 would have produced excessive inaccuracies in conversion. The method of curve fitting was essentially the same as that described on these pages.

[g] Curves cited for Peter Bent Brigham and Rhode Island represent those used when controls were 15 seconds. Because of the variability of prothrombin times for these hospitals, control figures for the day were taken into account in conversion. For equivalents used when other control times prevailed, see Part 2 of this table.

[h] Henry Ford used inactivated plasma as the diluent in prothrombin tests, therefore this curve based on inactivated plasma was used in conversion instead of that shown in Appendix Table 74 which employed saline as the diluent at the request of the Central Laboratory.

[i] Massachusetts General used beef lung thromboplastin, Rhode Island used human brain thromboplastin, and Mount Zion and San Francisco used both specially prepared rabbit brain thromboplastin and human brain thrombo[illegible]

[j] Used for daily control times of 15 [illegible]

[k] Used for da[illegible]

[l] Mount Zio[illegible] study period an[illegible] plastin. Human [illegible] 74, for explanat[illegible]

[m] Hospital c[illegible] [illegible]% or below for dilution curves submitted. Where tabulations required it, conversion intervals were estimated on an individual case basis by means of extrapolation.

APPENDIX TABLE 75, PART 2

SPECIAL PROTHROMBIN TIME CONVERSION TABLE USED FOR TIMES REPORTED BY RHODE ISLAND AND PETER BENT BRIGHAM HOSPITALS: Prothrombin Times Approximately Equivalent at Time of Study to Specified Intervals on Composite Dilution Curve Used as Standard in This Study and to Which Reported Prothrombin Times Were Converted When Rhode Island and Peter Bent Brigham Hospitals Reported Daily Control Figures at Given Levels

Prothrombin Time Interval on Composite Curve (Converted)[a]		Prothrombin Time Intervals for Specific Hospitals before Conversion (in seconds)[a] When Control Time (in seconds) Was—											
In Seconds	In Per Cent Prothrombin Activity	11	12	13	14	15	16	17	18	19	20	21	22
							Peter Bent Brigham						
Under 15	Over 100%	<11	<12	<13	<14	<15	<16	<17	<18	<19	<20	—[b]	—[b]
15-17	100 -58	11-14	12-15	13-16	14-18	15-19	16-20	17-21	18-22	19-23	20-24	—[b]	—[b]
18-19	57 -41	15-16	16-17	17-18	19-20	20	21-22	22-23	23-24	24-25	25-26	—[b]	—[b]
20-22	40 -28.3	17-19	18-20	19-21	21-23	21-24	23-25	24-27	25-28	26-29	27-32	—[b]	—[b]
23-24	28.2-23.7	20-21	21-22	22-23	24-25	25-26	26-27	28-29	29-31	30-32	33-36	—[b]	—[b]
25-29	23.6-16.8	22-24	23-26	24-28	26-29	27-31	28-34	30-37	32-39	33-42	37-51	—[b]	—[b]
30-34	16.7-13.2	25-27	27-29	29-31	30-33	32-36	35-43	38-46	40-48	43-56	52-[c]	—[b]	—[b]
35-39[c]	13.1-10.9[c]	28-31	30-33	32-35	34-36	37-41	44-52	47-57	49-60	57-[c]	—[c]	—[b]	—[b]
							Rhode Island						
Under 15	Over 100%	—[b]	<12	<13	<14	<15	<16	<17	<18	<19	<20	<21	<22
15-17	100 -58	—[b]	12-15	13-17	14-18	15-20	16-21	17-22	18-23	19-24	20-25	21-27	22-28
18-19	57 -41	—[b]	16-18	18-19	19-21	21-23	22-24	23-25	24-27	25-28	26-29	24-31	29-33
20-22	40 -28.3	—[b]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	31-40
23-24	28.2-23.7	—[b]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]-45
25-29	23.6-16.8	—[b]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]-53
30-34	16.7-13.2	—[b]	28-30	32-34	34-37	37-40	40-44	42-48	45-53	49-58	51-63	[illegible]	[illegible]-72
35-39[c]	13.1-10.9[c]	—[b]	31-34	35-38	38-41	41-44	45-49	49-56	54-63	59-72	63-80	87-89	73-91

[illegible] ...nts were not developed.
[illegible] ...lations required fit, the
[illegible] ...rapolation

APPENDIX TABLE 76

THROMBOEMBOLIC COMPLICATION RATES AT VARIOUS PROTHROMBIN LEVELS DURING DICUMAROL THERAPY: Number of Thromboembolic Complications Occurring at Various Prothrombin Levels from the Second Day of Dicumarol Therapy through the Day of the Last Dose and Number per Thousand Days Patients Were Maintained at These Levels among All Patients in the Total Sample Receiving Dicumarol

Prothrombin Time (Converted)[a]		Number of Days Observed at Given Levels[b]	Number of Thromboembolic Complications Occurring at Given Prothrombin Levels[b]		
			Total Number	Average Number per 1000 Days of Exposure to Risk at Given Prothrombin Levels	
In Seconds	In Per Cent Prothrombin Activity			As Reported	Weighted Average of Weekly Rates[c]
Under 20	41% or over	1,741	10	5.7[d]	5.5[d]
20-22	40-28.3	1,683	10	5.9	6.0
23-24	28.2-23.7	1,095	6	5.5	6.0
25-29	23.6-16.8	2,607	6	2.3	2.5
30-39	16.7-10.9	2,974	8	2.7	2.6
40-49	10.8-7.84	978	3	3.1	2.9
50 and over	7.83 and under	630	2	3.2	2.8
Total for all days of therapy with known readings		11,708	45	3.8	3.8
Total for days of unknown prothrombin times[e]		2,981	12[f]	4.0	—
Total for all days of dicumarol therapy		14,689	57	3.9	—

[a] For method of conversion, see pp. 350-352.

[b] Counts include and exclude the same data as those specified in footnote b of Table 140 of the text except that the first four days after the last dose of dicumarol are excluded.

[c] See footnote c of Table 140 of the text for explanation of the meaning of weighted average. The weighted averages were arrived at by computing rates for each prothrombin time interval for each week of the illness, weighting all weekly rates for a given level by the total known prothrombin readings (all levels) for the same week, summing the products, and dividing by the total weights.

[d] See footnote e of Table 140 of the text.

[e] See footnote f of Table 140 of the text.

[f] See footnote g of Table 140 of the text.

APPENDIX TABLE 77

PROTHROMBIN TIMES, BY WEEK OF ILLNESS: *Percentage of Prothrombin Readings Falling at Various Levels during the Entire Period of Dicumarol Therapy for All Types of Cases Receiving Dicumarol, by Week of Illness*

Prothrombin Time (Converted)[a]		Percentage of Usable Prothrombin Readings[b]						
In Seconds	In Per Cent Prothrombin Activity	All Weeks	Week of Illness					
			1st	2nd	3rd	4th	5th	6th
Under 15	Over 100%	1.0	4.1	.7	.2	.4	.5	.8
15–17	100–58	10.0	22.8	7.0	6.1	7.1	10.4	12.8
18–19	57–41	8.3	13.3	8.3	6.8	6.8	7.6	9.0
20–22	40–28.3	13.7	15.3	13.1	14 8	13.8	11.9	12.4
23–24	28.2–23.7	9.1	6.7	9.2	9.2	10.1	9.0	9.8
25–29	23.6–16.8	20.7	14.7	21.4	23.1	21.8	20.3	20.9
30–34	16.7–13.2	14 3	8.2	15 6	16 4	15.1	14.8	13.1
35–39	13.1–10.9	9.3	6.1	9 3	9.4	10.6	10.1	9.3
40–49	10.8–7 84	8 1	5.1	9 5	7.9	8.6	9.6	6.4
50–59	7.83–6 30	3.0	2.0	3 1	3.2	3.1	3.3	3.6
60 and over	6.29 and under	2 5	1.7	2.8	2.9	2.6	2.5	1.9
Total usable readings .		100.0	100 0	100.0	100.0	100.0	100.0	100.0
		Number of Usable[c] Prothrombin Readings						
All cases receiving dicumarol .		13,416	1,845	2,836	2,894	2,664	2,107	1,070

[a] For method of conversion, see pp. 350–352.

[b] Based on total number of usable readings. Period of therapy covered is that from day of the first *dose of dicumarol through the fourth day after the last dose* exclusive of interruptions in therapy during which the prothrombin time returned to normal Days of dicumarol therapy given control cases following the development of complications are included, but days when patients received heparin and days with prothrombin times that could not be converted are excluded.

[c] The total numbers of days of dicumarol therapy by week of illness are given in Appendix Table 36. *The difference between these totals and the figures here cited represent* days without prothrombin times, days with times that could not be converted, days with heparin, etc.

APPENDIX TABLE 78

PROTHROMBIN TIMES, BY HOSPITAL: Percentage of Prothrombin Readings for Treated Group Cases Falling at Various Levels from the Fourth Day of Dicumarol Therapy through the Day of the Last Dose and Mean and Median Prothrombin Times, by Hospital

Prothrombin Time (Converted)[a]		Percentage of Usable Prothrombin Readings from 4th Day of Dicumarol through Day of Last Dose[b]															
In Seconds	In Per Cent Prothrombin Activity	All Hospitals Whose Readings Could Be Converted[c]	Bellevue	Beth Israel	Cincinnati General	Cleveland City	Henry Ford	Jackson Memorial	Lakeside	Massachusetts General	Michael Reese	Mount Zion[d]	New York	Pennsylvania[c]	Peter Bent Brigham	Rhode Island	San Francisco[d]
Under 15	Over 100%	.3	.8	—	.4	2.1	.1	—	.4	—	—	1.3	.2	—	—	.1	—
15-17	100 -58	5.0	3.4	2.8	3.6	5.4	1.2	1.2	3.7	22.0	2.2	8.0	1.3	1.0	9.8	8.8	3.2
18-19	57 -41	7.0	5.4	7.1	3.5	5.9	3.7	2.8	4.3	19.3	5.2	20.9	.8	1.3	8.8	12.7	14.2
20-22	40 -28.3	13.9	4.4	27.3	19.6	8.6	4.4	5.3	11.5	20.0	12.0	31.4	5.3	3.8	20.3	21.4	27.8
23-24	28.2 -23.7	9.5	3.6	23.4	7.8	10.1	4.6	8.1	10.8	11.7	10.4	17.6	6.1	1.0	13.6	13.9	18.2
25-29	23.8 -18.8	22.9	14.1	32.9	20.1	23.1	17.8	24.2	31.9	10.8	23.2	15.1	35.3	11.3	25.3	22.6	19.9
30-34	18.7 -13.2	18.8	20.3	5.8	19.7	16.6	15.0	24.8	22.2	4.8	22.0	4.0	23.1	11.3	11.3	11.4	8.3
35-39	13.1 -10.9	10.4	11.6	1.0	10.0	12.3	18.0	15.5	9.5	.8	12.9	1.8	13.2	21.0	4.8	5.1	1.7
40-49	10.3 - 7.84	5.6	15.5	—	3.8	10.5	19.3	11.3	6.0	.4	9.6	.3	11.9	25.6	3.1	2.7	2.6
50-59	7.83- 6.30	3.1	13.1	—	.9	4.2	8.3	2.0	.7	.4	1.9	—	1.1	14.6	1.8	1.1	1.7
60 and over	6.29 and under	2.6	8.0	—	.6	1.7	6.9	4.8	.2	—	.6	—	.7	9.4	.4	.8	.2
Total usable readings[b]		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		Number of Usable Prothrombin Readings															
All treated cases receiving dicumarol ...		10,230	498	433	807	238	1,601	504	1,348	223	1,070	550	843	309	478	1,073	302
		Average Prothrombin Time															
Mean prothrombin time[e] ...		30	37	24	28	31	37	33	28	21	31	22	32	41	26	23	24
Median prothrombin time[f]		28	35	24	27	28	36	31	28	20	29	21	31	39	24	24	23

[a] For explanation of method of conversion, see p 330-332

[b] Percentages are based on the total number of usable prothrombin readings Tabulation omits periods of heparin therapy and periods when therapy was temporarily discontinued Unlike most other prothrombin tables, it also omits readings for control cases receiving anticoagulants as an exception

[c] Lack of dilution curves for normal blood appropriate to the period of treatment prevented the conversion of readings prior to August 1, 1947 for Pennsylvania Hospital and all readings for Veterans Hospital. For total days of anticoagulant therapy, add days with no readings days under heparin, similar days of therapy *for control cases*, and days of treatment for Veterans Hospital cases to the totals given here. Early Pennsylvania cases are tabulated here as unknown days.

[d] Due to early oversight in the statistical analysis, all conversions of prothrombin times for Mount Zion and San Francisco employed the conversion curve for rabbit brain thromboplastin shown in Appendix Table 74 although both hospitals used at varying times both rabbit brain and human brain thromboplastin The error was discovered so late that only partial corrections were feasible. To represent fairly the prevailing policies at these hospitals, the columns *for these hospitals* in this table have been fully corrected. To avoid excessive costs for minor late changes, the totals elsewhere utilize the earlier uncorrected conversions The resulting understatements of some prothrombin times are believed more than counterbalanced by the overstatements of prothrombin times that commonly result from hidden inaccuracies in laboratory determinations

[e] Based on ungrouped data.

[f] Based on grouped data. (See also footnote f, Appendix Table 79)

APPENDIX TABLE 79

PROTHROMBIN TIMES, BY LENGTH OF TIME UNDER DICUMAROL: Percentage of Pı thrombin Readings Falling at Various Levels and Average Prothrombin Times at Various Staı of Dicumarol Therapy for All Types of Cases Receiving Dicumarol

Prothrombin Time (Converted)[a]		Percentage of Usable Prothrombin Readings[b]										
			1st 3 Days of Dicumarol					Days after Last Dose of Dicumaro				
In Seconds	In Per Cent Prothrombin Activity	Total Period of Dicumarol Therapy	Total 1st 3 Days	1st Day[c]	2nd Day	3rd Day	4th Day through Day of Last Dose of Dicumarol	Total 1st 4 Days after Last Dose	1st Day after	2nd Day after	3rd Day after	4t Da aft
Under 15	Over 100%	1.0	6.5	14.8	4 8	1.2	.3	1.1	1.3	.6	1.8	
15-17	100-58	10.0	34.7	59.0	36.8	12.9	5 0	26.5	11.5	19.7	31.5	42
18-19	57-41	8.3	17.2	16.3	22.1	13.5	7.0	9.8	9.3	8 8	8.3	12
20-22	40-28.3	13 7	15.5	5 8	17.7	21.4	13.9	9.7	7.2	7.6	6.8	16
23-24	28.2-23.7	9 1	6.4	2.5	6.2	9.7	9.4	8 3	12.1	7.2	10.2	3
25-29	23.6-16.8	20.7	10.1	1.3	7.8	19.5	23.0	12 9	12.1	12.7	15.7	10
30-34	16.7-13.2	14.3	4.6	.3	2.7	9.7	16 4	7.3	9.7	9.4	7.4	2
35-39	13.1-10 9	9.3	2.2	—	1.4	4 8	10.4	7 0	13.1	6.7	5.6	2.
40-49	10.8-7.84	8.1	2.2	—	.5	5.6	8.8	8.7	14.6	13.0	5.6	1.
50-59	7.83-6.30	3.0	—	—	—	—	3.2	4.9	5 0	6 7	4.0	4.
60 and over	6 29 and under	2.5	.6	—	—	1.7	2.6	3.8	4.1	7.6	3.1	.
Total usable readings		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.
		Number of Usable Prothrombin Readings										
All cases receiving dicumarol		13,416[e]	1,310	393	435	482	10,791	1,315	321	330	324	340
		Mean Prothrombin Time[f]										
All cases receiving dicumarol		27.6	20.7	16.7	19.5	25.0	28.5	27.4	31.0	31.0	25.8	22.:

[a] For method of conversion, see pp 350-352.

[b] Based on total number of usable readings. Days of dicumarol therapy given control cases following the development of complications are included, but days when patients received heparin and days with prothrombin times that could not be converted are excluded

[c] The total numbers of days of dicumarol therapy by week of illness are given in Appendix Table 36. The difference between these totals and the figures here cited represent days without prothrombin times, days with times that could not be converted, days with heparin, etc

[d] Distributions were estimated since in most instances few or no prothrombin readings were reported after that for the day on which the last dose of dicumarol was received. Estimates were based on all available reports, namely, prothrombin readings for 190 patients for the first four days after the last dose (or until times were normal)

[e] A total of 16,766 days of dicumarol therapy was given but 3,350 of these were days without prothrombin times, days with times that could not be converted, days with heparin, etc.

[f] *Based on ungrouped data except for means for period after last dose which were based on grouped* data. Since no method for converting readings over 100% or below 6 25 per cent to a comparable base was available, all readings over 100 per cent were counted as 14 seconds in computing averages and all readings of 6.25% or less were counted as 60 seconds. Thus the influence of extremes on the arithmetic averages was artificially reduced.

APPENDIX TABLE 80

... [illegible] ...LATION TO TIME REQUIRED TO ... [illegible] ...ntage of Cases Receiving Various Com- ... [illegible] ... Days of Dicumarol Therapy and Having [U]sable Records Who First Reached Prothrombin Times of at Least 25 Seconds Specific Numbers of Days after the Beginning of Dicumarol Therapy

Doses of Dicumarol (in mg.) Received during First Three Days of Dicumarol Therapy			Number of Cases with Usable Records[a]	Percentage of Usable Cases First Reaching 25 Seconds on or before Following Days[b] of Dicumarol Therapy		
1st Day	2nd Day	3rd Day		4th Day	5th Day	6th Day
300	0	0	26	*62*	*69*	*85*
300	0	100	16	*50*	*56*	*81*
300	100	0	10	*58*	*63*	*95*
300	0	200	22	*55*	*82*	*91*
300	100	100	17	*53*	*59*	*71*
300	200	0	41	85	90	93
300	0	300	10	*70*	*90*	*90*
300	200	100	53	64	83	92
300	300	0	26	*77*	*85*	*96*
300	200	200	20	*45*	*75*	*85*
300	300	100	16	*56*	*69*	*88*
300	300	200	13	*77*	*92*	*92*
300	300	300	25	*80*	*96*	*100*
Total cases with above initial dosage sequences			304	66	80	90
All cases receiving other initial dosage sequences			151	46	55	63
Total usable cases[a]			455	59	71	81

Note. *Italics are used when percentages quoted are based on less than 30 cases since chance factors render such rates particularly unstable.*

[a] The following types of cases were not considered usable for this tabulation. cases in which the prothrombin times could not be converted to a basis comparable with other hospitals, cases for which prothrombin times were missing for specific days essential to ascertaining the first day 25 seconds was reached, cases receiving heparin during the early days of therapy, and cases treated less than 14 days and not reaching 25 seconds prior to the termination of therapy. The tabulation does include control group cases receiving dicumarol after the development of a thromboembolic complication (provided such cases meet the other criteria listed).

[b] Day counts are inclusive of first day of therapy and the day 25 seconds was reached. Twenty-five seconds (converted) is equivalent to 23 6 per cent prothrombin activity.

APPENDIX TABLE 81

DOSAGE IN INITIAL PERIOD IN RELATION TO TIME REQUIRED TO REACH 25 AND 30 SECONDS: Number of Cases Receiving Dicumarol and Having Usable Prothrombin Records First Reaching Prothrombin Times of 25 and 30 Seconds or Longer on *Specific Days of Dicumarol Therapy*, by Total Dosage of Dicumarol Received during the First Three Days of Dicumarol Therapy

Day of Dicumarol Therapy[a]	Number of Cases[b] First Reaching Specified Prothrombin Times on Specific Days of Dicumarol Therapy															
	25 Seconds (23.6 Per Cent or Less)								30 Seconds (16.7 Per Cent or Less)							
	All Usable Cases[b]	*Cases Receiving Total Dose of Dicumarol (in mg.) during First Three Days of Dicumarol Therapy of—*							All Usable Cases[b]	*Cases Receiving Total Dose of Dicumarol (in mg.) during First Three Days of Dicumarol Therapy of—*						
		100–299	300–399	400–499	500–599	600–699	700–799	800–999		100–299	300–399	400–499	500–599	600–699	700–799	800–999
1st	6	—	1	—	2	2	—	1	1	—	1	—	—	—	—	—
2nd	33	1	5	9	6	4	4	4	11	—	2	4	—	2	1	2
3rd	124	3	13	15	34	35	12	12	76	3	6	8	25	26	4	4
4th	106	2	8	18	30	27	6	15	75	—	4	13	14	21	10	13
5th	56	—	6	7	11	17	8	7	60	—	4	9	11	19	5	12
6th	44	1	7	13	7	10	5	1	45	—	6	7	13	12	5	2
7th	20	1	1	5	5	5	3	—	29	2	2	5	7	8	3	2
8th	12	—	2	3	3	3	1	—	21	—	3	5	7	2	2	2
9th or 10th	8	—	—	5	—	1	1	1	20	—	1	3	6	4	6	—
11th or 12th	10	1	6	1	1	—	1	—	12	1	4	4	1	—	1	1
13th or 14th	3	—	2	—	—	—	1	—	7	—	2	2	2	1	—	—
After 14th day	10	—	—	3	6	—	1	—	17	—	7	2	4	2	1	1
Never reached specified prothrombin time[b]	23	1	4	9	6	2	—	1	68	3	10	23	17	8	5	2
Total usable cases[b]	455	10	55	88	111	106	43	42	442	9	52	85	107	105	43	41

[a] Day counts are inclusive of first day of therapy and the day 25 or 30 seconds was reached. Twenty-five seconds (converted) is equivalent to 23.6 per cent prothrombin activity; 30 seconds (converted) is equivalent to 16.7 per cent prothrombin activity.

[b] The following types of cases were not considered usable for this tabulation: cases in which the prothrombin times could not be converted to a basis comparable with the other hospitals, cases for which the prothrombin times were missing for specific days essential to ascertaining the first day 25 or 30 seconds was reached, cases receiving heparin during the early days of therapy, and cases treated less than 14 days and not reaching 25 or 30 seconds prior to the termination of therapy. The tabulation does include cases treated less than 14 days if they reached 25 or 30 seconds before termination, cases treated more than 14 days and never reaching 25 or 30 seconds, and control groups cases receiving dicumarol after the development of a thromboembolic complication (provided such cases meet the other criteria listed). The cases suitable for the 30 second analysis differed slightly from those usable for the 25 second analysis.

APPENDIX TABLE 82

TOTAL DICUMAROL DOSAGE IN FIRST WEEK AND PROTHROMBIN TIME RESPONSE: Number and Percentage of Cases Who Received Various Total Amounts of Dicumarol during the First Week of Dicumarol Therapy Who Showed an Average Number of Seconds Increase in Prothrombin Times of Various Amounts from the Third through the Ninth Day of Dicumarol Therapy

Average Number of Seconds [illegible]	Cases with Usable Records[a] Receiving Dicumarol Nine Days or More							
	[illegible]	[illegible]	[illegible]	[illegible] or Over	[illegible]	[illegible]	[illegible]	[illegible] or Over
Less than 8 0	33	49	37	30	41	36	29	31
8 0-15 9	24	56	56	39	30	41	41	41
16 0 or more	23	32	34	27	29	23	27	28
Total usable[c] cases . .	80	137	127	96	100	100	100	100

[a] See footnote a, Table 146 of the text.
[b] See footnote b, Table 146 of the text.
[c] See footnote c, Table 146 of the text
[d] Based on total usable cases in subgroup

APPENDIX TABLE 83

AVERAGE PROTHROMBIN [illegible]

[illegible] (Converted),[b] [illegible]		Total Cases	Cases Receiving Dicumarol One Week or Less[e]	Cases Receiving Dicumarol for More than One Week and in Average[d] Daily Doses (in mg) of —											
In Seconds	In Per Cent Prothrombin Activity			30-39	40-49	50-59	60-69	70-79	80-89	90-99	100-109	110-119	120-129	130-139	140 and Over
15 0-17 9	100-52%	11	3	—	—	—	2	—	1	2	1	—	1	—	1
18 0-19 9	51-37 6	23	—	—	—	5	5	5	3	3	—	—	—	1	1
20 0-22.9	37 5-26.9	63	1	—	3	11	9	14	5	6	7	5	2	—	—
23 0-24 9	26.8-22 6	66	—	3	7	9	5	9	6	11	4	5	5	1	1
25 0-29.9	22 5-16 3	155	7	1	7	17	22	28	20	15	13	15	8	1	1
30 0-34 9	16 25-12 81	109	3	—	4	11	16	23	15	12	9	8	5	1	2
35 0-39 9	12 80-10 58	71	2	2	1	4	14	10	15	6	7	4	3	3	—
40 0-44.9	10 57-8 89	33	1	2	2	—	2	3	2	2	10	7	1	—	1
45 0 and over	8.88 and under	10	4	—	1	—	—	2	1	1	1	—	—	—	—
Average prothrombin time unknown[e]		68	45	1	1	—	3	4	3	2	2	5	2	—	—
Total cases receiving dicumarol[f]		609	66	9	26	57	78	98	71	60	54	49	27	7	7

[a] Arithmetic means covered all usable times from 4th day of dicumarol through day of last dose. Geometric means might have been used to reduce the excessive effect on the averages of occasional high prothrombin times (in seconds) often produced with relatively small doses of dicumarol, but for over 500 cases the cost would have been prohibitive. To achieve roughly similar results [illegible] over 60 seconds were counted as 60 only in computing [illegible]
[b] For [illegible] the [illegible]
[d] [illegible]
[e] In some cases prothrombin readings could not be converted (see footnote c, Appendix Table [illegible]
[f] Counts include control cases receiving dicumarol but exclude [illegible]

APPENDIX TABLE 84

FIRST UNDILUTE PROTHROMBIN READINGS: Number and Percentage of First Undilute Pr thrombin Readings for All Cases in the Sample Taken after the Attack and before the Beginnin of Anticoagulant Therapy (if Any) Falling at Various Levels and Corresponding Distributions o Prothrombin Readings for the Blood of Normal Persons Tested under Corresponding Laborator Conditions

Prothrombin Time (Converted)[a] Undilute Plasma		Coronary Thrombosis Cases (First Readings Taken after the Attack and before the Beginning of Anticoagulant Therapy (if Any)—All Usable Readings For the Total Sample)[b]		Normal Persons Whose Blood Was Tested under Corresponding Laboratory Conditions[c]	
In Seconds	In Per Cent Prothrombin Activity	Number of Readings	Per Cent of Readings	Number of Readings	Per Cent of Readings
Under 15	Over 100%	70	13.4	101	19.3
15	100	97	18.5	228	43.6
16	92-72	105	20.1	119	22.7
17	71-58	87	16.6	32	6.1
18	57-48	54	10.3	26	5.0
19	47-41	46	8.8	13	2.5
20	40-36	29	5.5	3	.6
21	35-32	17	3.3	—	—
22	31-28.3	5	1.0	—	—
23	28.2-25.8	6	1.1	1	.2
24	25.7-23.7	1	.2	—	—
25	23.6-21.8	—	—	—	—
26	21.7-20.3	—	—	—	—
27	20.2-19.0	—	—	—	—
28	18.9-17.9	2[d]	.4	—	—
29	17.8-16.8	1	.2	—	—
30	16.7-16.0	—	—	—	—
31	15.9-15.0	—	—	—	—
32	14.9-14 4	—	—	—	—
33	14.3-13.7	1	.2	—	—
—	—	—	—	—	—
40	10.8-10.4	1[d]	.2	—	—
41	10.3-10.0	1[d]	.2	—	—
Total usable readings . .		523	100 0	523	100.0

[a] For method of conversion, see pp. 350-352.

[b] First readings were not considered usable: (1) if they were taken on the second day of anticoagulant therapy or thereafter (readings on the first day of anticoagulants were considered usable since inquiry indicated that such readings were taken routinely prior to the first dose of dicumarol); (2) if the first reading was taken on the first day of anticoagulants and heparin was given on the same day; (3) if readings were taken under circumstances that did not permit conversion (see footnote c, Appendix Table 78); (4) if the conversion procedures adopted for the hospital in question provided for the use of the control reading for the day as 100% (Rhode Island, Peter Bent Brigham, and Massachusetts General; see Appendix Table 75) since the same procedure applied to normal blood would render all converted normal blood times for these hospitals 100% or 15 seconds; (5) if the readings were from hospitals not reporting daily control figures and no other normal blood readings run in the same laboratory under corresponding conditions could be substituted (Mount Zion and San Francisco Hospitals); or, (6) if uncertainty existed regarding the prothrombin time reported.

[c] The data reported for normal blood were compiled as follows: 229 normal blood readings (control times) taken on the same days and under the same laboratory conditions as for the coronary cases and converted by the same procedures (all such readings reported) were supplemented, in order to . . . hospitals with few or no undilute control readings, by the addition of . . . onnection with the dilution curve study (see Appendix Table . . . is representative of the period of the study for the hos- . . . Single readings or averages of two readings were selected from the dilution curve

readings The total was further augmented by the addition of 61 readings for The New York Hospital distributed in the same manner as 828 readings for normal undilute blood had been found to be dis- ... more or less representation ... curves for each hos- ... with weights that re- ... same total readings as ... nearest possible approach to comparability, are artificial.

[f] First prothrombin readings for these cases were taken within three days of death. One case with an undilute prothrombin time of 40 seconds had Laennec's cirrhosis of the liver.

APPENDIX TABLE 85

FIRST DILUTE PROTHROMBIN READINGS: Number and Percentage of First Dilute Prothrombin Readings for All Cases in the Sample Taken after the Attack and before the Beginning of Anticoagulant Therapy (if Any) Falling at Various Levels and Corresponding Distributions of Prothrombin Readings for the Blood of Normal Persons Tested under Corresponding Laboratory Conditions

Prothrombin Time (Converted)[a] Dilute Plasma (12.5 per cent)		Coronary Thrombosis Cases (First Readings Taken after the Attack and before the Beginning of Anticoagulant Therapy (if Any)—All Usable Readings for the Total Sample)[b]		Normal Persons Whose Blood Was Tested under Corresponding Laboratory Conditions[c]	
In Seconds	In Per Cent Prothrombin Activity	Number of Readings	Per Cent of Readings	Number of Readings	Per Cent of Readings
21-22	35-23 3%	6	1.7	4	1.2
23-24	23.2-23.7	7	2.0	2	.6
25-26	23 6-20.3	23	6 7	11	3.2
27	20 2-19.0	14	4.1	3	.9
28	18.9-17.9	15	4.4	5	1.4
29	17.8-16.8	18	5.3	12	3.5
30	16.7-16.0	24	7 0	10	2.9
31	15.9-15.0	21	6.1	22	6.4
32	14.9-14.4	30	8.8	15	4.4
33	14.3-13.7	18	5 3	19	5.5
34	13.6-13.2	23	6.7	44	12.9
35	13.1-12 7	11	3.2	28	8.2
36	12 6-12.2	13	3.8	29	8.5
37	12.1-11.7	18	5 3	25	7.3
38	11.6-11.3	11	3.2	45	13.2
39	11.2-10.9	11	3.2	16	4.7
40-41	10.8-10 0	24	7.0	22	6.4
42-43	9 9-9 31	13	3 8	24	7.0
44-45	9 30-8.72	10	2 9	3	.9
46-47	8.71-8.30	5	1.5	—	—
48-49	8.29-7.84	4	1.2	—	—
50-51	7.83-7.46	5	1.5	3	.9
52-55	7.45-6.81	4	1.2	—	—
56-59	6.80-6 30	5	1 5	—	—
60 and over	6.29 and under	9	2.6	—	—
Total usable readings		342	100.0	342	100.0

[a] For method of conversion, see pp. 350-352.

[b] For definition of usable readings see footnote b, Appendix Table 84. Usable dilute prothrombin readings were available only for Bellevue, Beth Israel, Cleveland City, Henry Ford, Jackson Memorial, Lakeside, Michael Reese, and New York Hospitals.

[c] For method of ... readings for the ... of 83 readings fro... similar to those ...

APPENDIX TABLE 86

ORGANS EXAMINED AT AUTOPSY: Percentage of Autopsy Reports That Included Gross ar Microscopic Reports on Given Organs for All Cases and for Cases Receiving and Not Receiving Anticoagulants

Organ Examined	Percentage of Autopsy Reports That Included Reports on Given Organs[a]					
	All Cases (89 Cases)		Cases Receiving No Anticoagulants (48 Cases)		Cases Receiving Anticoagulant (41 Cases)	
	Gross[b] Reports	Microscopic Reports	Gross[b] Reports	Microscopic Reports	Gross[b] Reports	Microscopic Reports
Heart	100	99	100	98	100	100
Aorta	89	56	85	54	93	59
Lungs	99	94	100	96	98	93
Brain	37	21	46	25	27	17
Gastrointestinal tract	85	57	90	63	81	51
Liver	91	89	94	92	88	85
Kidneys	90	87	94	92	85	81
Spleen	89	83	94	88	83	78
Pancreas	89	78	96	81	81	73
Adrenal glands	87	73	94	79	78	66
Prostate[c]	84	62	89	58	78	67
Testes[c]	67	35	67	33	44	37
Uterus[d]	88	62	92	67	86	57
Vessels of arms	2	—	2	—	2	—
Vessels of legs	10	1	8	2	12	—

[a] For actual number of organs examined, see Appendix Tables 89 and 90.

[b] In the few instances where gross autopsy reports failed to mention organs for which there was a microscopic report, it was assumed that mention was omitted because no pathology was found on gross examination and the organs were therefore included in the gross counts. Gross totals used for percentages thus represent total organs examined.

[c] Percentages are based on total males in subgroup.

[d] Percentages are based on total females in subgroup.

APPENDIX TABLE 87

EXTENT OF DESCRIPTION IN AUTOPSY REPORTS: Number and Percentage of Gross and Microscopic Autopsy Reports on Specific Organs in Which the Report Was in Descriptive Form and the Number That Were Summaries Only

Type of Report Received	Total Number of Reports on Specific Organs[a]					
	All Cases		Cases Not Receiving Anticoagulants		Cases Receiving Anticoagulants	
	Gross Reports	Microscopic Reports	Gross Reports	Microscopic Reports	Gross Reports	Microscopic Reports
Reports with description	782	528	427	249	355	279
Reports with summary only	102	206	73	161	29	45
Total reports	884	734	500	410	384	324
	Percentage of Organ Reports Given in Descriptive Form					
Total organs examined	88	72	85	61	92	86

[a] Organs included are those listed in Appendix Table 86. Units were defined in terms of the organ [illegible] unit. [illegible] [illegible]uded.

APPENDIX TABLE 88

LOCATION OF ORIGINAL INFARCTION AND ORIGINAL OCCLUSION AS FOUND AT AUTOPSY: Number of Original Myocardial Infarctions Found at Autopsy in Various Chambers and Areas in Which Specific Coronary Arteries Were Found Occluded

Chambers and Areas Involved	Number of Original Infarctions[a]				
	Total	Coronary Artery, Total or Partial Occlusion of Which Produced the Infarction			
		Left or Its Branches Only	Right or Its Branches Only	Both Left and Right and Their Branches	Not Specified or No Apparent Focus
Anterior only:					
Left ventricle and septum	26	25	—	—	1
Left and right ventricle and septum	1	1	—	—	—
Left ventricle only	5	5	—	—	—
Right ventricle only	1	1	—	—	—
Septum only	1	—	1	—	—
Total, anterior only	34	32	1	—	1
Posterior only:					
Left ventricle and septum	9	2	7	—	—
Left and right ventricle and septum	10	1	7	2	—
Left ventricle only	8	4	3	—	1
Septum only	2	—	2	—	—
Total, posterior only	29	7	19	2	1
Both anterior and posterior:[b]					
Left ventricle and septum	10	6	—	4	—
Left and right ventricle and septum	5	3	—	2	—
Left and right ventricle	1	—	—	1	—
Septum only	4	2	1	—	1
Total, both anterior and posterior	20	11	1	7	1
Anterior-posterior location not specified:					
Left ventricle and septum	4	2	—	1	1
Left and right ventricle and septum	—	—	—	—	—
Left ventricle only	1	1	—	—	—
Chamber not specified	1	—	—	1[c]	—
Total, anterior-posterior location not specified	6	3	—	2	1
All original infarctions	89	53	21	11	4
Total infarctions involving—					
Left ventricle	80	50	17	10	3
Right ventricle	18	6	7	5	—
Septum	73	42	18	10	3

[a] Counts exclude extensions and new secondary myocardial infarctions; hence only one infarction was tabulated per case. When the infarctions involved one or more ventricles as well as the septum, the anterior-posterior classification represents the location of the infarction in the ventricles rather than in the septum. Involvements of the apex also were not considered in making the classification.

[b] Includes various possible combinations, such as anterior in one chamber and posterior in the other, or both locations in the same or both chambers.

[c] This infarction involved the septum.

APPENDIX TABLE 89

LOCATION AND CORRECTNESS OF CLINICAL DIAGNOSIS OF EXTRACARDIAC THROMBOEMBOLIC COMPLICATIONS FOUND AT AUTOPSY: Number of Cases Found to Have Thromboembolic Complications in Various Locations outside the Heart at Autopsy and Number of Such Complications Found among Cases Receiving and Not Receiving Anticoagulants, by Correctness of Clinical Diagnosis of Complications

Location	Number of Autopsies in Which Organ Was Examined	Extracardiac Thromboembolic Complications Found at Autopsy							
		Number of Cases with One or More Complications				Number of Complications			
		Found at Autopsy	Diagnosed Clinically: Confirmed at Autopsy	Diagnosed Clinically: Not Confirmed at Autopsy	Not Diagnosed Clinically	Found at Autopsy	Diagnosed Clinically: Confirmed at Autopsy	Diagnosed Clinically: Not Confirmed at Autopsy	Not Diagnosed Clinically
	Cases Not Receiving Anticoagulants								
Lungs	48	11	5	1	6	18	7	1	11
Kidneys	45	8	—	—	8	14	—	—	14
Brain	22	1	1	1	—	1	1	1	—
Spleen	45	1	—	—	1	1	—	—	1
Adrenal glands	45	—	—	—	—	—	—	—	—
Liver	45	1	—	—	1	1	—	—	1
Aorta	41	5	—	—	5	11	—	—	11
Other arteries	—[a]	—	—	—	—	—	—	—	—
Leg veins	4	2	—	—	2	4	—	—	4
Other veins	—[a]	4	—	—[b]	4	10	—	—[b]	10
	Cases Receiving Anticoagulants								
Lungs	40	3	1	1	2	4	2	3	2
Kidneys	35	2	—	—	2	2	—	—	2
Brain	11	1	—	—	1	1	—	—	1
Spleen	34	2	—	—	2	2	—	—	2
Adrenal glands	32	1	—	—	1	1	—	—	1
Liver	36	—	—	—	—	—	—	—	—
Aorta	38	2	—	—	2	4	—	—	4
Other arteries	—[a]	—	—	—[c]	—	—	—	—[c]	—
Leg veins	5	—	—	—[d]	—	—	—	—[d]	—
Other veins	—[a]	2	—	—	2	4	—	—	4

[a] It was impossible to count the total number of cases in which other arteries and other veins in specific areas were examined.

[b] One case was found to have two venous thromboses clinically, one in the left antecubital vein and one in the left jugular vein. These are not reported here since the specific veins were not examined at autopsy. However, a venous thrombosis was found at autopsy in the left subclavian vein *which may* have been related to one of those diagnosed clinically.

[c] *One case with a peripheral embolus in the right arm diagnosed clinically is not reported here since the vessels of the arm were not examined at autopsy.*

[d] One case with two venous thromboses (one in each leg) and one case with a venous thrombosis in the right calf are not reported here since the leg veins were not examined at *autopsy*.

APPENDIX TABLE 90

SPECIFIC ORGANS SHOWING HEMORRHAGE AT AUTOPSY: Number of Organs in Cases Receiving and Not Receiving Anticoagulants Examined at Autopsy in Which Hemorrhage Was Found on Gross Examination and on Microscopic Examination Only (Including Cardiac Rupture Cases)

Organs Examined	Organs Examined Grossly[a]				Organs Examined Both Grossly and Microscopically[b]							
	Number of Each Organ Examined		Number in Which Hemorrhage Was Found on Gross Examination		Number of Each Organ Examined		Number in Which Hemorrhage Was Found					
							Total		On Gross Examination		On Microscopic Examination Only	
	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants	Cases Receiving No Anticoagulants	Cases Receiving Anticoagulants
Heart[c]	43	41	25	27	47	41	29	35	24	27	5	8
Other organs:												
Brain	22	11	—	—	12	7	2[d]	—	—	—	2[d]	—
Lungs	48	40	2[e]	1[f]	46	38	5[e]	3[f, g]	2[e]	1[f]	3[e]	2[g]
Aorta	41	38	—	1[h]	26	24	2[i]	1[j]	—	—	2[i]	1[j]
Gastrointestinal tract	43	33	4[k]	3[l]	30	21	3[m]	3[n]	3[m]	2[n]	—	1[o]
Liver	45	36	—	—	44	33	—	—	—	—	—	—
Gall bladder	45[p]	36[p]	—	1	44[p]	35[p]	—	1	—	1	—	—
Spleen	45	34	—	—	42	32	1[q]	2[q]	—	—	1[q]	2[q]
Pancreas	46	33	1	—	39	30	1	1	1	—	—	1
Adrenal glands	45	32	—	—	38	27	—	1	—	—	—	1
Kidneys	45	35	2[r]	3[s]	44	38	2[r]	5[s]	2[r]	3[s]	—	2
Bladder	45[t]	35[t]	2[u]	—	44[t]	33[t]	4	—	2[u]	—	2[v]	—
Prostate	32	21	—	—	21	18	—	—	—	—	—	—
Testes	24	12	—	1	12	10	—	1	—	1	—	—
Uterus	11	12	—	1	8	8	—	1	—	1	—	—
Total, other organs	537	408	11	11	450	351	20	19	10	9	10	10
Total, all organs[w]	585	449	36	38	497	392	49	54	34	36	15	18

[a] Includes organs examined grossly only and those examined both grossly and microscopically.
[b] Excludes organs examined grossly only.
[c] Excluding cardiac ruptures *per se* but including hemorrhages associated with rupture and other intracardiac hemorrhages in rupture cases.
[d] One in the cerebral cortex and one in the pia arachnoid.
[e] The two hemorrhages apparent on gross examination were associated with infarctions and accompanied by hemothorax; one of the hemorrhages apparent only microscopically was also associated with an infarction.
[f] One hemorrhage was associated with an infarction
[g] One hemorrhage was associated with severe congestion.
[h] A petechial hemorrhage of the ascending aorta.
[i] One was a subintimal hemorrhage of the abdominal aorta and one was a medial hemorrhage of the ascending aorta.
[j] An adventitial hemorrhage of the aorta.
[k] Including one in the stomach, one in the duodenum, and two involving most of the gastrointestinal tract. One was associated with congestion and one with gastritis.
[l] Two in the large and small bowel (one associated with marked congestion) and one in the stomach.

footnotes to table 90 continued on next page

footnotes to table 90 continued

[m] One in the duodenum and two in the gastrointestinal tract (*one associated with marked congestion* and one with gastritis).

[n] The two apparent on gross examination were in the large and small bowel, one associated with marked congestion.

[o] The hemorrhage apparent microscopically only occurred in the mucosa of the esophagus.

[p] Counts of the number of gallbladders examined assumed that the gallbladder was examined whenever the liver was mentioned as examined.

[q] All hemorrhages in the spleen were associated with congestion.

[r] One of these was associated with a recent infarction of the kidney.

[s] *One of these was associated with a recent infarction of the kidney* and one with marked congestion.

[t] Counts of the number of bladders examined assume that the bladder was examined whenever the kidneys were mentioned as examined.

[u] One of these cases had cystitis.

[v] Two of these cases had cystitis.

[w] Total counts do not agree with Appendix Table 87 because estimated counts for gallbladder and bladder have been added and vessels of arms and legs are not counted as organs.

APPENDIX TABLE 91

COMPARISON OF CLINICAL AND AUTOPSY FINDINGS ON A CASE BASIS: Listing of Clinical Diagnoses, Corresponding Autopsy Findings, Other Major Autopsy Findings, and Related Circumstances for Each Case in the Total Series Submitted to Autopsy

A—anticoagulant therapy
No A—no anticoagulant therapy
LV—left ventricle
RV—right ventricle
S—interventricular septum
BPI—onset before present illness
M—multiple

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week		
1 (No A)	Male 71 years old Died 2nd day No anticoagulants	Inside heart Infarct—posteroseptal (1) History of Infarct (5 wks before onset) Outside heart Congestive heart failure—moderate left and right (1-2)	*Inside heart* Infarct, massive, hemorrhagic—posterior wall of LV, posterior ½ of S, anterior and posterior papillary muscles, unspecified portions of RV noted microscopically Mural thrombus—anteromedial wall of right auricle Aneurysmal dilatation—LV just beneath mitral valve and at apex Fibrosis of healed infarct (BPI)—posterior wall of LV, posterior portion of S Outside heart Hydrothorax Congestion—lungs, abdominal viscera Ascites Renal infarct, healing (BPI)—right kidney	Patient became cyanotic preceding death.
2 (No A)	Male 77 years old Died 3rd day No anticoagulants	Inside heart Infarct—septal (1) Outside heart Shock, severe (1-3) Congestive heart failure—moderate left (1-3)	Inside heart Infarct, massive—anterior, lateral, and posterior walls of LV including apex, anterior portion of S Mural thrombus, large—LV including septal wall Pericarditis, fibrinous Outside heart Hydrothorax Congestion—lungs, abdominal viscera Pulmonary edema Subcutaneous edema	Patient in semistupor 2nd and 3rd days

APPENDIX TABLE 91 (cont.)

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, If Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
2 (No A) (cont.)		Hemiplegia from cerebrovascular accident in the distribution of the right middle cerebral artery Pneumonia, hypostatic—right	Cerebral swelling presumed by the pathologist to be due to the myocardial infarction (only gross examination of the brain reported for this case) Pneumonia, lobular Cholelithiasis and cholecystitis	
3 (No A)	Male 59 years old Died 3rd day No anticoagulants	Inside heart: Infarct—anteroseptal (1) Outside heart.	Inside heart: Infarct—anterior and lateral walls of LV, lower ⅔ of anterior portion of S Mural thrombus—LV Pericarditis, fibrinous Scars of healed infarct (BPI)—same area as recent infarct Outside heart. Congestion—lungs, liver, spleen, brain	Clinical statement that cause of death was "cardiac arrest, continuing infarction"
4 (A)	Male 50 years old Died 3rd day Heparin (1) Dicumarol (1-2) (see last column)	Inside heart: Infarct—posterior (1) Outside heart: Shock, severe (1-3)	Inside heart. Infarct—posterior portion of S Pericarditis, fibrinous Outside heart: Congestion—lungs, liver, spleen, kidneys	Clinical report states "The morning of the 3rd day the prothrombin time was 45. By that afternoon a few hours before death, in spite of Vitamin K, his prothrombin time had risen to 120 secs. undilute. The patient was in profound shock with heart block and forward failure. We have never been able to explain this terrific response to a small dosage of dicumarol We believe that the extensive rise in the level may have been due to the heart block with forward failure, failure of circulation to the liver, and hence the inability of the liver to manufacture prothrombin."
5 (A)	Male 60 years old Died 3rd day Dicumarol (2)	Inside heart: Infarct—diffuse changes (1) Outside heart: Shock, severe (1-3)	Inside heart Infarct—posterior wall of LV, posterior portion of S Mural thrombus—apex of LV Healing infarct (BPI)—posterior wall of LV at apex Outside heart: Hydrothorax Congestion—abdominal viscera Pulmonary edema Renal infarct, healed (BPI) Cholelithiasis	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, If Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
6 (A)	Female 80 years old Died 3rd day Heparin (2) Dicumarol (2)	Inside heart. Infarct—posterior (1) Outside heart. History of Diabetes mellitus, uncontrolled Right cerebrovascular accident (2 weeks before onset) Gallbladder disease	Inside heart: Infarct, hemorrhagic—posterior and lateral walls of LV Rupture, incomplete—from myocardium into pericardial sac in infarcted area 3 cm. from apex Hemopericardium Outside heart Hydrothorax Congestion—lungs, abdominal viscera Atelectasis Mural thrombus—lower aorta (attached to atheromatous plaque) Not confirmed (only gross examination of the brain reported for this case) Cholecystitis	Died suddenly when blood pressure was being taken.
7 (A)	Male 62 years old Died 3rd day Dicumarol (2)	Inside heart *Infarct*—posterior (1) Outside heart Shock, mild (1-3) Congestive heart failure—mild left (1-3) Hemoptysis, mild (2)	Inside heart Infarct—posterior wall of LV Pericarditis, fibrinopurulent Outside heart. Hydrothorax Congestion—lungs, abdominal viscera Pulmonary edema Bronchopneumonia, terminal Adrenal infarct, recent—right	
8 (No A)	Male 74 years old Died 4th day No anticoagulants	Inside heart. Infarct—no definite localization could be made because of ventricular tachycardia (1) Outside heart	Inside heart. Infarct—LV and S, but more specific location not reported Mural thrombus—right auricular appendage Pericarditis Fibrosis of healed infarct (BPI)—S Outside heart Pulmonary emboli (M) and infarcts (4), recent—right lung Pneumonia, lobular, confluent—all lobes Hydrothorax Pulmonary edema Congestion—lungs, abdominal viscera Cholelithiasis and cholecystitis	After some improvement, the patient died suddenly. *Clinically it* was considered that possibly ventricular tachycardia was responsible.

APPENDIX TABLE 91 (cont.)

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, If Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
9 (No A)	Male 46 years old Died 4th day No anticoagulants	Inside heart: Infarct—anteroseptal (1) Outside heart: Bronchopneumonia or infarction of right lower lobe of lungs	Inside heart: Infarct, massive—entire LV, anterior ¾ of S Mural thrombi—LV, RV, right auricle Pericarditis, adhesive Outside heart: Pneumonia, lobular—right lower lobe Pulmonary edema Congestion—lungs, abdominal viscera Leptomeningitis and congestion of cerebral vessels	Patient had Adams Sto syncopal attacks.
10 (No A)	Male 73 years old Died 4th day No anticoagulants	Inside heart: Infarct—anterior (1) Pericardial friction rub (3–4) Outside heart. Shock, moderate (1–4) Congestive heart failure—moderate left (1–4) Bronchopneumonia	Inside heart. Infarct—anterior and lateral walls of LV, anterior ½ of S Mural thrombus—LV including septal wall Pericarditis, fibrinous Fibrosis of healed infarcts (2) (BPI)—one in anterior wall of LV; the other in posterior wall of LV and posterior portion of S Outside heart Hydrothorax Congestion—abdominal viscera Pulmonary edema Bronchopneumonia—all lobes	
11 (No A)	Male 74 years old Died 4th day No anticoagulants	Inside heart: Infarct—anterior (1) Outside heart Shock (onset on 3rd day but degree and duration not indicated) Abdominal bleeding with hematemesis, moderate (3) History of Thrombophlebitis	Inside heart Infarct—entire wall of LV and S Mural thrombus—apex of LV Outside heart: Congestion—lungs, spleen Pulmonary edema No source found for bleeding from autopsy report Atelectasis	
12 (No A)	Male 70 years old Died 4th day No anticoagulants	Inside heart Infarct—anterior (1) History of Infarct (about 1 month before onset) Outside heart: Shock, severe (4) Congestive heart failure—moderate left and right (1–4)	Inside heart Infarct—LV, RV, and S, but more specific location not reported (Since the occlusion is located in the anterior descending branch of the left coronary artery, the infarct is probably anterior) Pericarditis, fibrinous Fibrosis of healed infarct (BPI)—anterior wall of LV *Outside heart* Congestion—lungs, liver, spleen Cholelithiasis and cholecystitis	

APPENDIX TABLE 91 (cont.)

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, If Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
13 (A)	Male 69 years old Died 4th day Dicumarol (2-3)	Inside heart: Infarct—posterior (1) History of Infarct (1½ yrs before onset) Outside heart Probable embolus in right brachial artery (3) Congestive heart failure—left, degree not specified (4)	Inside heart: Infarct, hemorrhagic—posterior wall of LV Scarring of healed infarct (BPI)—posterior wall of LV near apex Outside heart Artery not dissected out at autopsy Congestion—lungs, liver, spleen Pulmonary edema Subcutaneous edema	On 3rd day patient complained of sudden pain in right arm. Brachial and radial pulses were absent.
14 (A)	Male 37 years old Died 4th day Dicumarol (2-3)	Inside heart Infarct—anteroseptal (1) History of: Infarct—posterior (6 wks before onset) Outside heart Shock, moderate (1-4) Pneumonia—bilateral	Inside heart: Infarct with marginal hemorrhage—anterior wall of LV, anterior portion of S Pericarditis, fibrinous Fibrosis of healed infarct (BPI)—anterior wall of LV, anterior portion of S Outside heart Pulmonary edema Congestion—lungs, liver, spleen, kidneys	Following the development of complete A-V block, the patient had numerous convulsive seizures (Stokes-Adams) and died during one of them. Ventricular fibrillation terminally.
15 (No A)	Male 66 years old Died 5th day No anticoagulants	Inside heart Infarct—diffuse changes (1) Outside heart Shock, moderate (5) Congestive heart failure—severe left (5) Hematemesis (1) Laennec's cirrhosis of liver History of Cerebral accident with left hemiplegia (year before onset)	Inside heart Infarct—entire LV and S Mural thrombi—LV and RV Outside heart: Congestion—lungs, abdominal viscera Pulmonary edema Pneumonia, lobular Varices—esophageal, gastric, urinary Portal cirrhosis of liver Hepatic infarct Brain not examined	Patient died suddenly. For 15 years patient had been drinking about a quart of whiskey a day. He developed Laennec's cirrhosis of the liver. A prothrombin reading taken on the 3rd day of this illness was 40 secs. undilute.
16 (No A)	Male 64 years old Died 5th day No anticoagulants	Inside heart Infarct—anterior (1) History of. Infarct (4 yrs before onset) Outside heart Congestive heart failure, progressive—mild to severe left (1-5) History of Pernicious anemia for 22 yrs	Inside heart Infarct, hemorrhagic—anterior wall of LV, lower ⅔ of S Fibrosis and scarring of healed infarct (BPI)—posterior and lateral walls of LV Outside heart Hydrothorax Congestion—lungs Pulmonary edema Thrombus—aorta proximal to bifurcation (attached to atheromatous plaque) Cholelithiasis and cholecystitis	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
Cases Dying during the First Week (cont.)				
9 (No A)	Male 45 years old Died 4th day No anticoagulants	Inside heart: Infarct—anteroseptal (1) Outside heart: Bronchopneumonia or infarction of right lower lobe of lungs	Inside heart: Infarct, massive—entire LV, anterior ⅔ of S Mural thrombi—LV, RV, right auricle Pericarditis, adhesive Outside heart: Pneumonia, lobular—right lower lobe Pulmonary edema Congestion—lungs, abdominal viscera Leptomeningitis and congestion of cerebral vessels	Patient had Adams-Stokes syncopal attacks.
10 (No A)	Male 73 years old Died 4th day No anticoagulants	Inside heart: Infarct—anterior (1) Pericardial friction rub (3-4) Outside heart: Shock, moderate (1-4) Congestive heart failure—moderate left (1-4) Bronchopneumonia	Inside heart: Infarct—anterior and lateral walls of LV, anterior ½ of S Mural thrombus—LV including septal wall Pericarditis, fibrinous Fibrosis of healed infarcts (2) (BPI)—one in anterior wall of LV; the other in posterior wall of LV and posterior portion of S Outside heart: Hydrothorax Congestion—abdominal viscera Pulmonary edema Bronchopneumonia—all lobes	
11 (No A)	Male 74 years old Died 4th day No anticoagulants	Inside heart Infarct—anterior (1) Outside heart Shock (onset on 3rd day but degree and duration not indicated) Abdominal bleeding with hematemesis, moderate (3) History of Thrombophlebitis	Inside heart: Infarct—entire wall of LV and S Mural thrombus—apex of LV Outside heart Congestion—lungs, spleen Pulmonary edema No source found for bleeding from autopsy report Atelectasis	
12 (No A)	Male 70 years old Died 4th day No anticoagulants	Inside heart: Infarct—anterior (1) History of Infarct (about 1 month before onset) Outside heart: Shock, severe (4) Congestive heart failure—moderate left and right (1-4)	Inside heart Infarct—LV, RV, and S, but more specific location not reported (Since the occlusion is located in the anterior descending branch of the left coronary artery, the infarct is probably anterior) Pericarditis, fibrinous Fibrosis of healed infarct (BPI)—anterior wall of LV Outside heart Congestion—lungs, liver, spleen Cholelithiasis and cholecystitis	

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
20 (No A) (cont.)			autopsy, but size and condition of infarct were compatible with it. Also there was a fresh extension of the thrombus found in the anterior descending branch of the left coronary artery Perivascular hemorrhage—anterior descending branch of left coronary artery Mural thrombus—right ventricle Pericarditis, fibrinous and adhesive	
		Outside heart	Outside heart Hydrothorax Pulmonary edema Congestion—lungs, abdominal viscera Atelectasis	
		Renal disease	Renal thrombi (M)—recent and old (BPI) Right kidney surgically absent Embolus in artery of spleen, old (BPI)	
		Gallbladder disease	Cholelithiasis	
21 (No A)	Male 66 years old Died 6th day No anticoagulants	Inside heart Infarct—posterior (1) History of Infarct—anterior (about 2 months before onset)	Inside heart Infarct—posterior ¾ of S Pericarditis, fibrinous Fibrosis of healed infarct (BPI)—anterior wall of LV, anterior portion of S Mural thrombus, old (BPI)—anterior wall of LV and S Aneurysmal dilatation—LV	
		Outside heart: Shock with forward failure of heart, severe (5-6)	Outside heart *Autopsy of chest only* Hydrothorax Congestion—lungs Pneumonia, lobular, focal Atelectasis	
22 (A)	Male 62 years old Died 6th day Dicumarol (4)	Inside heart Infarct—posterior and diffuse changes (1)	Inside heart Infarct, hemorrhagic—posterior wall of LV, posterior portion of S Rupture, incomplete—from myocardium into pericardial sac in posterior wall of LV Hemopericardium Mural thrombus—posterior wall of LV	
		Pericardial friction rub (4)	Pericarditis, fibrinous	
		Outside heart Shock, moderate (4-6) Congestive heart failure—moderate right (2-6)	Outside heart Congestion—lungs (liver not examined) Pulmonary edema Atelectasis	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, If Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
17 (A)	Female 73 years old Died 5th day Dicumarol (2-3)	Inside heart: Infarct—anterior (1) History of. *Infarct (6 months before onset)* Rheumatic heart disease *Ventricular tachycardia (5)* Outside heart: Congestive heart failure—*moderate right (1-5)*	Inside heart: *Infarct—anterior and lateral walls of LV, lower ⅔ of S* Pericarditis, fibrinous *Fibrosis of healed infarct (BPI)—same area as recent infarct* Scarring of rheumatic heart disease, together with mitral stenosis and insufficiency Outside heart. Hydrothorax Congestion—lungs, liver Pulmonary edema Cerebral edema	Patient had ventricular tachycardia of 2 hrs 45 min. duration before death. Clinically it was considered that probably ventricular fibrillation occurred terminally.
18 (A)	Female 69 years old Died 5th day Dicumarol (3-5)	Inside heart: Infarct—anterior (1) *Pericardial friction rub (5)* Outside heart: History of: *Thrombosis of central artery of left retina (3 yrs before onset)* *Possible small arterial embolus to right leg (2 yrs before onset)*	Inside heart Infarct—posterior and lateral walls of LV Rupture, complete—very small *opening in posterior wall of LV just beneath mitral valve* Hemopericardium Pericarditis, fibrinous *Fibrosis of healed infarct (BPI)—LV, but more specific location not reported* Outside heart: *Congestion—lungs, abdominal viscera*	Patient moved from one room to another on a stretcher 5 hrs before death.
19 (A)	Female 64 years old Died 5th day Dicumarol (3-4)	Inside heart Infarct—anterior (1) Outside heart: Congestive heart failure—*moderately severe left and right (1-5)* History of: Diabetes mellitus, mild (discovered 5 yrs before onset)	Inside heart: Infarct with marginal hemorrhage—lower ¼ of S and adjacent tip of LV Pericarditis, fibrinous Outside heart: *Autopsy of heart only* Hydrothorax	
20 (No A)	Male 80 years old Died 6th day No anticoagulants	Inside heart: Infarct—anterior (1) Probable extension of infarct (6)	Inside heart: Infarct, massive—greater portion *of LV, including apex;* almost entire S, posterior wall of RV Extension diagnosed clinically could not be distinguished at	Patient appeared to be doing quite well with no evidence of cardiac failure or vascular collapse when he expired suddenly.

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
26 (No A) (cont.)		Outside heart Shock, severe (1-7) Congestive heart failure—moderate left and severe right (1-7) History of: Cerebral accident with right hemiplegia Diabetes mellitus	Outside heart· Hydrothorax Congestion—lungs, liver, kidneys Subcutaneous edema Brain not examined	
27 (No A)	Male 80 years old Died 7th day No anticoagulants	Inside heart Infarct—EKG showed only right bundle branch block (1) History of Infarct (4 yrs before onset) Outside heart Congestive heart failure—mild left and moderate right (1-7) History of Cerebral accident with left hemiparesis (4 yrs before onset following myocardial infarct)	Inside heart Infarct, hemorrhagic—entire LV, apex of RV, posterior portion of S Mural thrombus—apex of RV Pericarditis, fibrinous No definite evidence of old infarct but areas of fibrosis in myocardium Outside heart Hydrothorax Congestion—lungs, liver, spleen Subcutaneous edema Bronchopneumonia—left Renal infarcts (M), old (BPI) Cortex of brain shows destruction of normal structures with large empty spaces traversed by a small amount of fibrillar material Encephalomalacia Cerebral edema	
28 (No A)	Male 55 years old Died 7th day No anticoagulants	Inside heart· Infarct—anteroseptal (1) Possible rupture of myocardium History of Infarct—posterior (by EKG reading taken this illness, time of occurrence not known) Outside heart Congestive heart failure—mild right (4-7)	Inside heart Infarct—S Pericarditis, fibrinous No definite evidence of old infarct but areas of fibrosis and old occlusions Outside heart Hydrothorax Congestion—lungs, liver Pulmonary edema Ascites Pulmonary infarct, recent, small—right lung	Died suddenly.
29 (A)	Female 54 years old Died 7th day Dicumarol (2-4)	Inside heart· Infarct—anterior (1) Outside heart	Inside heart Infarct, hemorrhagic—anterior and lateral walls of LV Rupture, complete—anterolateral aspect of LV Hemopericardium Mural thrombus—anterior wall of LV Outside heart Congestion—liver, spleen Mural thrombi (M)—aorta (on scattered ulcers)	Patient had brief convulsion lasting a few seconds and then died suddenly.

APPENDIX TABLE 91 (cont.)

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
23 (A)	Male 66 years old Died 6th day Heparin (1-2) Dicumarol (1-4)	Inside heart: Infarct—posterior (1) History of: Infarct (4 yrs before onset) Outside heart: Congestive heart failure—moderate left (3-6), moderate right (4-6)	Inside heart: Infarct—posterior walls of LV and RV, posterior portion of S Pericarditis—fibrinopurulent No definite evidence of old infarct but fibrosis of myocardium present in area of recent infarction Outside heart. Hydrothorax Congestion—lungs, liver, spleen, kidneys Pulmonary edema	
24 (A)	Male 53 years old Died 6th day Dicumarol (4)	Inside heart· Infarct—anterior (1) Pericardial friction rub (4-6) Outside heart. Jaundice (5-6) Congestive heart failure—moderate right (3-6)	Inside heart Infarct, hemorrhagic—anterior apex of LV, anterior portion of S Rupture, incomplete—from myocardium into pericardial sac in anteroapical portion of LV along S Hemopericardium Pericarditis, fibrinous Outside heart *Autopsy of chest only* Hydrothorax Congestion—lungs	Patient experienced onset of precordial pain 4 days before death.
25 (A)	Female 62 years old Died 6th day Dicumarol (5)	Inside heart Infarct—diffuse changes Outside heart Congestive heart failure—left and right, degree not reported (1-6)	Inside heart Infarct, hemorrhagic—apex of LV and distal 3 cm of apex of RV Rupture, incomplete—from myocardium into pericardial sac in center of apical infarct Hemopericardium Pericarditis, fibrinous Fibrosis and scarring of healed infarct (BPI)—posterior wall of LV Outside heart. Hydrothorax Congestion—lungs, liver, spleen Pulmonary edema Renal infarct with marginal hemorrhage, recent—right kidney	Patient became cyanotic and died
26 (No A)	Female 66 years old Died 7th day No anticoagulants	Inside heart Infarct—posterior (1) Pericardial friction rub (5-7)	Inside heart Infarct—posterior wall of LV Fibrosis and scarring of healed infarct (BPI)—S, anterior wall and apex of LV	

o	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the First Week (cont.)		
1) .)		Outside heart *Shock, severe (1-7)* Congestive heart failure—moderate left and severe right (1-7) History of Cerebral accident with right hemiplegia Diabetes mellitus	Outside heart: Hydrothorax Congestion—lungs, liver, kidneys Subcutaneous edema Brain not examined	
A)	Male 80 years old *Died 7th day* No anticoagulants	Inside heart Infarct—EKG showed only *right bundle branch block* (1) History of *Infarct* (4 yrs before onset)	Inside heart Infarct, hemorrhagic—entire LV, apex of RV, posterior portion of S Mural thrombus—apex of RV Pericarditis, fibrinous No definite evidence of old infarct but areas of fibrosis in myocardium	
		Outside heart Congestive heart failure—mild left and moderate right (1-7) History of Cerebral accident with left *hemiparesis* (4 yrs before onset following myocardial infarct)	Outside heart Hydrothorax Congestion—lungs, liver, spleen *Subcutaneous edema* Bronchopneumonia—left Renal infarcts (M), old (BPI) Cortex of brain shows destruction of normal structures with large empty spaces traversed by a small amount of fibrillar material Encephalomalacia Cerebral edema	
28 (o A)	Male *85 years old* Died 7th day No anticoagulants	Inside heart Infarct—anteroseptal (1) Possible rupture of myocardium History of Infarct—posterior (by EKG reading taken this *illness*, time of occurrence not known)	Inside heart Infarct—S *Pericarditis, fibrinous* No definite evidence of old infarct but areas of fibrosis and old occlusions	*Died suddenly.*
		Outside heart Congestive heart failure—mild right (4-7)	Outside heart Hydrothorax Congestion—lungs, liver Pulmonary edema Ascites Pulmonary infarct, *recent*, small—right lung	
29 (A)	Female 84 years old Died 7th day Dicumarol (2-4)	Inside heart Infarct—anterior (1)	Inside heart *Infarct*, hemorrhagic—anterior and lateral walls of LV Rupture, complete—anterolateral aspect of LV Hemopericardium Mural thrombus—anterior wall of LV	Patient had brief convulsion lasting a few seconds and then died suddenly.
		Outside heart	Outside heart Congestion—liver, spleen Mural thrombi (M)—aorta (on scattered ulcers)	

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Second Week		
30 (No A)	Male 53 years old Died 8th day No anticoagulants	Inside heart Infarct—posterior (1) New secondary infarct—*anterolateral and right ventricular* (7) Pericardial friction rub (3 and 8) Paroxysmal auricular and *ventricular tachycardia* (7) History of Infarct (5 yrs before onset) Outside heart Shock, moderate (1-8) Diabetes, mild	Inside heart: Infarct—posterior walls of LV and RV, posterior portion of S Extension of infarct, hemor-*rhagic*—same area as above and extending to anterolateral border Mural thrombus—posterior wall of LV Pericarditis, fibrinous Fibrosis of healed infarct (BPI)—anterior papillary muscle Outside heart Congestion—lungs, abdominal viscera *Pulmonary edema* Subcutaneous edema Bronchopneumonia, early Atelectasis Renal infarcts (M), old (BPI)	
31 (No A)	Male 53 years old Died 8th day No anticoagulants	Inside heart *Infarct—posterior* (1) *Extensions of myocardial infarct* (4 and 8) Outside heart Shock, moderate (4-8) Congestive heart failure—moderate left (4-8) *Cerebrovascular accident* with left hemiplegia (clinically thought probably due to embolus) (4) History of Luetic heart disease with aortitis and decompensation (chancre found 41 yrs before)	Inside heart *Infarct—posterior ½ of S* and adjacent ½ of posterior walls of LV and RV *Extensions* diagnosed clinically could not be distinguished at autopsy from the original infarct, but the extent and condition of the infarcted area could be compatible with an extension Pericarditis, fibrinous, hemorrhagic with 75 cc of serosanguineous fluid (hydropericardium) Outside heart Congestion—liver, spleen *Moderate sclerosis of Circle of* Willis, but no lesions found (only gross examination of the *brain reported in this case)* Mural thrombus—aorta Syphilitic aortitis with aneurysmal dilatation of ascending aorta Cholecystitis and cholelithiasis	
32 (No A)	Male 77 years old Died 8th day No anticoagulants	Inside heart Infarct—*anteroseptal* and posteroseptal (1) Pericardial friction rub (4-6)	Inside heart *Infarct*—anterior and posterior walls of LV in the apical portion, anterior and posterior *portions of S* Pericarditis, fibrinous	Patient became comatose and died

APPENDIX TABLE 91 (cont.)

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Second Week (cont.)		
32 (No A) (cont.)		Outside heart Congestive heart failure—moderate left and mild right (1-8) Pneumonia, lobular (8)	Outside heart Congestion—lungs, spleen Pulmonary edema Bronchopneumonia, focal	
33 (No A)	Male 61 years old Died 8th day No anticoagulants	Inside heart Infarct—posterior (1) Outside heart	Inside heart Infarct, hemorrhagic—posterior portion of S and adjacent areas of posterior walls of LV and RV Outside heart *Autopsy of chest only*	Patient found dead in bed. There were no premonitory symptoms. Clinically terminal ventricular fibrillation speculated as cause of death
34 (A)	Male 64 years old Died 8th day Dicumarol (7-8)	Inside heart Infarct—posterior (1) Outside heart Congestive heart failure—moderate left (7-8), mild right (6-8) Uremia—NPN 92 (8)	Inside heart Infarct—posterior wall of LV, posterior portion of S Mural thrombus—apex of LV Pericarditis, fibrinous Fibrosis of healed infarct (BPI)—anterior wall of LV Mural thrombus, organized (BPI)—right ventricle Outside heart Hydrothorax Congestion—lungs, abdominal viscera Pulmonary edema Atelectasis	
35 (A)	Male 47 years old Died 9th day Heparin (2-5) Dicumarol (2-7)	Inside heart Infarct—posterior (1) History of Infarcts (2) (about 10 months and 13 months before onset) Outside heart Shock, mild (2-8) Congestive heart failure, intermittently—mild to moderate left (2-8) mild right (7-8) Uremia—NPN 173 (7)	Inside heart Infarct—anterior wall of LV, anterior portion of S Hemorrhage, interstitial—myocardium Mural thrombus—anterior wall of LV and anterior portion of S No definite evidence of old infarct but areas of fibrosis and an old occlusion Outside heart Congestion—lungs, liver, spleen Pulmonary edema	Died during Stokes-Adams seizure.
36 (No A)	Female 43 years old Died 9th day No anticoagulants	Inside heart Infarct—anteroseptal (1) Pericardial friction rub (5-6) Outside heart Shock, moderate (5-9) Congestive heart failure—moderate left and mild right (5-9)	Inside heart Infarcts (M)—S, anterior and lateral walls of LV Mural thrombus—LV Pericarditis, fibrinous Scarring of healed infarct (BPI)—location not specified in report Outside heart Hydrothorax Congestion—lungs, abdominal viscera, severe	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
Cases Dying during the Second Week (cont.)				
36 (No A) (cont.)			Hemorrhage—small amount of fluid hemorrhage in pancreas; mucosa of duodenum slightly hemorrhagic Atelectasis	
37 (No A)	Male 54 years old Died 9th day No anticoagulants	Inside heart. Infarct—anteroseptal (1) Outside heart	Inside heart: Infarct—apical ⅔ of anterior wall of LV, anterior portion of S Mural thrombus—anterior wall of LV Pericarditis, fibrinous Rheumatic heart disease, *chronic, with mitral stenosis* Outside heart: Congestion—lungs, abdominal viscera Renal infarcts (2), recent—left kidney Atelectasis Cholecystitis Mural thrombi—aorta (at ulcerated points)	
38 (No A)	Female 55 years old Died 9th day No anticoagulants	*Inside heart* Infarct—posterior (1) Outside heart	*Inside heart:* Infarct—posterior wall of LV and posterior portion of S Extension of infarct, with marginal hemorrhage—same area as original plus lateral wall of LV Outside heart Hydrothorax	Patient died *suddenly.*
39 (A)	Male 63 years old Died 9th day Dicumarol (1-6)	Inside heart Infarct—anteroseptal (1) Outside heart Shock, severe (1-9) Congestive heart failure—severe right (9) Uremia, progressive Hematuria, moderate	Inside heart Infarct—anterior wall of LV, anterior portion of S Pericarditis, fibrinous Outside heart Hydrothorax Congestion—lungs, abdominal viscera Pulmonary edema Subcutaneous edema Bronchopneumonia, minimal Hemorrhage—mucosa of gastrointestinal tract, with 300 cc of dark red or brown contents in stomach and similar material throughout the *GI* tract	Patient in semistupor and unable to swallow *during* last three days.
40 (A)	Male 63 years old Died 9th day Dicumarol (6-7)	Inside heart Infarct—anterior (1)	Inside heart Infarct—anterior wall of LV, anterior portion of S Extension of infarct Hemorrhage, interstitial—myocardium	Clinical statement "At first, with high temperature, was thought to have pneumonia and diagnosis of coronary thrombosis was not

APPENDIX TABLE 91 (cont.)

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Second Week (cont.)		
40 (A) (cont.)			Rupture, complete—anterior wall of LV, running parallel to S Hemopericardium Mural thrombus—anterior apex of LV	made till 4th hospital day. Dicumarol probably given too late and for too short a time to have any effect."
		Pericardial friction rub (5)	Pericarditis, fibrinous Fibrosis of healed infarct (BPI)—location not reported	
		Outside heart Congestive heart failure—mild right and moderate left (1-9)	Outside heart *Autopsy of chest only* Hydrothorax Congestion—lungs Pulmonary edema Subcutaneous edema	
41 (No A)	Male 72 years old Died 10th day No anticoagulants	Inside heart Infarct—anterior (1)	Inside heart Infarct, hemorrhagic—S, papillary muscles, anterior and posterior walls of LV Mural thrombus—apical portion of LV Pericarditis, fibrinous	
		Outside heart Congestive heart failure—moderate right (6-9) moderate to severe left, progressive (6-10)	Outside heart Hydrothorax Congestion—lungs, liver, spleen, kidneys Bronchopneumonia Pulmonary thrombi (M) Cholelithiasis	
42 (A)	Female 45 years old Died 10th day Dicumarol (7)	Inside heart Infarct—anterior (1)	Inside heart. Infarct, hemorrhagic—apex of anterior wall of RV with aneurysmal dilatation at this point	On the 8th day severe pain recurred with shock, dyspnea and cyanosis. The pain persisted and the patient went steadily downhill
		Ventricular paroxysmal tachycardia (10)		
		Outside heart Shock, *moderately* severe to severe (8-10) Congestive heart failure—mild to severe left and moderate to moderately severe right (8-10)	Outside heart Hydrothorax Congestion—lungs, liver, spleen Pulmonary edema Thrombosis of right internal carotid artery, recent	
43 (A)	Female 63 years old Died 10th day Dicumarol (8)	Inside heart Infarct—EKG readings open to several interpretations 1—old posterior and new anterior 2—new posterior and anterior 3—new posterior and old anterior	Inside heart Infarct—anterior and posterior walls of LV, S Mural thrombus—posterior wall of LV and S Fibrosis and scarring of healed infarct (BPI)—posterior wall of LV, posterior portion of S	In spite of usual measures to combat pulmonary edema, the patient died in progressive congestive failure.

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
Cases Dying during the Second Week (cont.)				
43 (A) (cont.)		*Outside heart:* Congestive heart failure—moderate left and mild right (7-10)	*Outside heart:* Hydrothorax; Congestion—lungs, liver; Pulmonary edema; Bronchopneumonia—right upper lobe; Pulmonary infarct—right lower lobe	
		History of: Suspected cerebral hemorrhage with diffuse cortical atrophy (about 4 yrs before onset)	Atelectasis; Encephalomalacia; Cerebral edema	
			Thrombosis of pelvic veins, recent; Cholelithiasis	
44 (A)	Male; 47 years old; Died 10th day; Dicumarol (2-7)	*Inside heart:* Infarct—anterior (1)	*Inside heart:* Infarct—anterior wall of LV, anterior ⅔ of S, anterior wall of RV adjoining S; Mural thrombus—apex of LV	Clinically death was attributed to pneumonia. Patient did not rally to penicillin treatment
		Pericardial friction rub (3)	Pericarditis, fibrinous	
		Outside heart: Bronchopneumonia with bloody sputum	*Outside heart:* *Autopsy of chest only*; Bronchopneumonia, confluent—bilateral; Hydrothorax	
45 (No A)	Male; 57 years old; Died 11th day; *No anticoagulants*	*Inside heart:* Infarct—anterior (1)	*Inside heart:* Infarct, hemorrhagic—S, anterior papillary muscle; Mural thrombi—apex of LV, left auricular appendage; Fibrosis and scarring of healed infarct (BPI)—S	
		Paroxysmal auricular fibrillation (9-11)		
		Outside heart: Congestive heart failure—moderate left and mild right (7-11)	*Outside heart:* Hydrothorax; Pulmonary edema; Congestion—lungs, abdominal viscera; Thrombosis of adrenal vein; Cholelithiasis	
46 (No A)	Female; 65 years old; Died 11th day; No anticoagulants	*Inside heart:* Infarct—anterior (1)	*Inside heart:* Infarct—S, anterior and posterior wall of LV, left auricular appendage	
		Extension—posterior and lateral (5)	Extension diagnosed clinically could not be distinguished at autopsy but size and condition of infarct were compatible with it; Pericarditis, fibrinous	
		Outside heart: Congestive heart failure—severe right (5-7)	*Outside heart:* Hydrothorax; Congestion—lungs; Pulmonary edema; Subcutaneous edema; Ascites	
		Shock, degree not reported (11)		

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Second Week (cont.)		
47 (No A)	Male 39 years old *Died 11th day* No anticoagulants	Inside heart Infarct—anterior (1) Pericardial friction rub (2) Outside heart	Inside heart Infarct—anterior wall of LV, anterobasal ½ of S Extension of infarct Mural thrombus—anterior LV and anterior S Pericarditis, fibrinous Outside heart Congestion—lungs, liver, spleen, kidneys Renal infarct, recent—right kidney	Patient died suddenly.
48 (No A)	Male 74 years old Died 11th day No anticoagulents	Inside heart Infarct—anterior (1) Outside heart *Congestive* heart failure—severe left (time of occurrence not reported)	Inside heart Infarct—apex of LV, anterior ½ of S Outside heart Congestion—lungs, abdominal viscera Pulmonary edema Atelectasis Cerebral edema and congestion Encephalomalacia	Ventricular premature beats first observed day before death.
49 (A)	Female 55 years old *Died 11th day* Dicumarol (2-4)	Inside heart Infarct—anteroseptal (1) Outside heart Congestive heart *failure*— mild right (2-11) mild left (10-11) Uremia—*NPN 200* Anuria	Inside heart Infarct—*anterior* wall of LV in vicinity of apex Rupture, septal—from LV into *RV in funnel-shaped thinned* area near apex Outside heart Congestion—lungs, liver, spleen Subcutaneous edema	Clinically the death of the *patient was felt* due primarily to the great fall in blood pressure with consequent diminished cerebral and renal blood flow resulting in anuria and uremia.
50 (No A)	Male *56* years old Died 12th day No anticoagulants	Inside heart Infarct—anterior (1) New secondary infarct—*posterior (9)* Possible rupture terminally Outside heart *Possible* pulmonary embolus terminally	Inside heart Infarct—S, anterior wall of LV New secondary infarct—posterior wall of LV Mural thrombus—apex of LV Pericarditis, fibrinous Outside heart Hydrothorax Congestion—lungs, liver, spleen, kidneys Pulmonary edema Pneumonia, lobular	Died very suddenly after complaining of some pain *in chest which clinically* was attributed to a possible rupture of the myo*cardium* or a pulmonary embolus
51 (No A)	Male 75 years old Died 12th day No anticoagulants	*Inside* heart Infarct—posterior (1)	Inside heart Infarct, massive—posterior wall of LV, *posterior* portion of S Pericarditis, adhesive	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Second Week (cont.)		
51 (No A) (cont.)		*Outside heart:* Congestive heart failure—moderate left and right (7-12) *Possible* pulmonary infarct—consolidation of right lung base (7) Uremia	Outside heart: Hydrothorax Congestion—lungs, abdominal viscera Pulmonary edema Pneumonia, lobular—right lung and left lower lobe, confluent Cholecystitis Cerebellar infarct, healed (BPI)	
52 (A)	Male 61 years old Died 12th day Dicumarol (1-11)	Inside heart: Infarct—anterior (1) *Outside heart:* Congestive heart failure—severe to mild left (1-12)	*Inside heart:* Infarct—anterior wall of LV, anterior ½ of S *Outside heart:* *Hydrothorax* Congestion—lungs, liver, spleen, kidneys Pulmonary edema Pulmonary thrombus—right lung Atelectasis Laennec's cirrhosis of liver	Patient appeared to b making steady progre toward recovery but w found dead in bed. *In the light of clinical an* autopsy findings, th pathologist considere death must have resulte from some acute fun tional failure such a ventricular fibrillation
53 (A)	Male 51 years old *Died 12th day* *Dicumarol (1-10)*	Inside heart Infarct—anterior (1) Pericardial friction rub (2) Outside heart Congestive heart failure—moderate left (2-12) Hemoptysis, mild, due to passive congestion of lungs (3) Progressive abdominal distention (5-12)	Inside heart: Infarct—anterior wall of LV, anterior portion of S Pericarditis, fibrinous Outside heart Hydrothorax Pulmonary edema Congestion—abdominal viscera Subcutaneous edema Atelectasis Colitis, catarrhal, acute	Disoriented, cyanotic, an severe abdominal di tention the day befor death
54 (No A)	Male 62 years old Died 13th day No anticoagulants	Inside heart. Infarct—anterior (1) Pericardial friction rub (2) Extension of infarct (8) *Outside heart* Pulmonary embolus (3) Bronchopneumonia Renal failure with uremia	Inside heart *Infarct*—anterior and *posterior* walls of LV, S Mural thrombus—LV Pericarditis, fibrinous *Outside* heart Pulmonary embolus and infarct—right lung Hydrothorax Congestion—liver, spleen Bronchopneumonia Pneumonia, lobular Atelectasis Renal infarct, healing—left kidney Thrombosis of left renal artery	
55 (No A)	Male 67 years old Died 13th day No anticoagulants	Inside heart. Infarct—anterior (1)	Inside heart *Infarct—anterior wall of LV,* anterior portion of S Mural thrombi—LV, left auricular appendage Pericarditis, fibrinous	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Second Week (cont.)		
55 (No A) (cont.)		Outside heart Pulmonary embolus (5) Hemoptysis (question of pulmonary infarction raised) (5) Bronchopneumonia History of Diabetes mellitus (diabetic ketosis found during this illness)	Outside heart Pulmonary thrombus—vein in left lung Bronchopneumonia—all lobes Hydrothorax Congestion—liver, spleen Venous thrombi (M)—right popliteal veins	
56 (A)	Female 79 years old Died 13th day Dicumarol (9-10)	Inside heart Infarct—posterior (1) History of Infarcts (3) (about 6 months, 2 yrs, and 10 yrs before onset) Outside heart Congestive heart failure—moderate left with acute terminal episode (2-13)	Inside heart Infarct, hemorrhagic—posterior portion of S and adjacent posterior walls of LV and RV Pericarditis, fibrinous Scarring of healed infarcts (M) (BPI)—anterior wall of LV at apex; posterior portion of S and adjoining posterior walls of LV and RV Outside heart Hydrothorax Congestion—lungs, liver Atelectasis	
57 (No A)	Female 74 years old Died 14th day No anticoagulants	Inside heart Infarct—anterior (1) Outside heart Cerebral embolus (7) History of Diabetes mellitus (discovered 3 yrs before onset)	Inside heart Infarct—anterior wall and apex of LV Mural thrombus—apex of LV Pericarditis, fibrinous Outside heart Cerebellar infarct, recent (number not clear, but at least one) Pulmonary infarct, organizing—left lung Pulmonary edema Renal thrombi (M), recent—small arteries of kidney pelvis Renal infarct, recent—left kidney Infarct of spleen, recent	
58 (No A)	Female 81 years old Died 14th day No anticoagulants	Inside heart Infarct—septal (1) Outside heart Shock, moderate (8-14) Congestive heart failure—moderate left and right (8-14) Uremia—BUN 82 History of Diabetes mellitus (for 20 yrs prior to onset)	Inside heart Infarct—S, anterior and posterior walls of LV Mural thrombus—anterior LV Outside heart Hydrothorax Congestion—lungs, liver Subcutaneous edema Cholelithiasis and cholecystitis	

APPENDIX TABLE 91 (cont.)

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, If Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Second Week (cont.)		
59 (A)	Male 75 years old Died 14th day Dicumarol (5-7)	Inside heart: Infarct—anteroseptal (1) Pericardial friction rub (9) Outside heart: Hematuria, moderately severe (due to acute hemorrhagic cystitis and related to high levels of prothrombin time secondary to dicumarol)	Inside heart: Infarct, hemorrhagic—anterior wall of LV, anterior portion of S Subepicardial hemorrhages with small amount of hemopericardium Mural thrombus—LV Pericarditis, fibrinous Fibrosis of healed infarcts (M) (BPI)—posterior walls of LV and RV Outside heart: Pulmonary edema Congestion—lungs, abdominal viscera Bronchopneumonia, hypostatic—bilateral Renal emboli (M), old (BPI) Cardiac cirrhosis of liver Cystitis, acute, hemorrhagic	
60 (A)	*Male* 70 years old Died 14th day Dicumarol (4-13)	*Inside heart* Infarct—anterior (1) Pericardial friction rub (2) Outside heart: Shock, severe (14) Pulmonary infarct or pneumonic consolidation (3) Spread of pneumonia in right lung (13)	*Inside heart:* Infarct—anterior wall of LV Extension of infarct, hemorrhagic Mural thrombi—apex of LV; through patent foramen ovale into both auricles Pericarditis, fibrinous Outside heart Hydrothorax Congestion—lungs, abdominal viscera	*Terminally* patient had severe dyspnea, lung rales, but no pain. Died in 30 minutes
		Cases Dying during the Third Week		
61 (No A)	Male 48 years old Died 15th day No anticoagulants	Inside heart. Infarct—anteroseptal (1) *Extension of infarct (11)* Outside heart Shock, severe (11-15) Congestive heart failure—mild left (14-15)	Inside heart Infarct—lower ½ of S and adjacent anterior wall of LV Rupture, septal—in center of infarcted area Mural thrombus—S Pericarditis, fibrinous Outside heart Hydrothorax Congestion—lungs, liver, kidneys Urinary bladder mucosa hemorrhagic focally	On the 11th day the patient had an acute episode of severe pain which seemed like an extension of the infarct but EKG readings showed no evidence of it

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, If Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Third Week (cont.)		
62 (No A)	Female 79 years old Died 18th day No anticoagulants	Inside heart Infarct—posteroseptal (1) Rupture of S (8)	*Inside heart* Infarcts (M), massive—throughout myocardium Rupture, septal (no details reported) Mural thrombi, *old* and *recent*—LV, RV Hemopericardium (source not indicated, only a summary of autopsy findings was submitted)	On the 8th day the patient developed a loud systolic *murmur* which was thought clinically to be perforation of the interventricular septum
		Outside heart *Bronchopneumonia*—*right* Possible pulmonary infarct Jaundice, slight (11) Uremia History of Cerebral accident (no details *reported*)	Outside heart Pulmonary emboli and infarcts (M)—right lung and left lower lobe Congestion—abdominal viscera Thrombosis of iliac, perivesicle, uterine, bladder, right renal and right ovarian veins Cardiac cirrhosis of liver Brain not examined	Patient admitted to hospital because of pneumonia *in right lower lobe*
63 (No A)	Male 63 years old Died 18th day No anticoagulants	Inside heart Infarct—posterior (1) Extension of infarct (16) Pericardial friction rub (5)	Inside heart Infarct—posterior and lateral walls of LV, posterior portion *of* S Extension of infarct Pericarditis, fibrinous Fibrosis and scarring of healed infarct (BPI)—posterior wall of LV, posterior portion of S Bernheim syndrome—almost occluding RV cavity and related to healed infarct Hemopericardium—fresh granular blood clots, most marked over the base posteriorly and at the *left* margin (no source indicated)	
		Outside heart Congestive heart failure—mild left terminally	Outside heart Congestion—lungs, liver, kidneys Pulmonary edema Subcutaneous edema *Renal infarcts (M)*, recent, with marginal hemorrhage	
64 (No A)	Female 49 years old Died 16th day No anticoagulants	Inside heart Infarct—posterior (1)	Inside heart Infarct—posterior portion of S, posterior papillary muscles, posterior and lateral walls of LV	Patient had a sudden substernal pain radiating to left arm and died 2 hrs later.
		Outside heart	Outside heart Congestion—lungs, abdominal viscera Bronchopneumonia, slight—bilateral Cholelithiasis and cholecystitis	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Third Week (cont.)		
63 (No A)	Male 67 years old Died 18th day No anticoagulants	Inside heart: Infarct—anterior (1) History of: Infarct—posterior (3 wks prior to onset) Outside heart: History of: Diabetes mellitus	Inside heart: Infarct—S, anterior and apical portions of LV Fatty infiltration of RV, marked Fibrosis of healed infarct (BPI)—posterior wall of LV Outside heart: Congestion—lungs, liver, spleen, kidneys Pulmonary edema	Patient first considered to suffer from gastrointestinal obstruction or cardiospasm because of continued anorexia and vomiting
65 (A)	Male 41 years old Died 16th day Dicumarol (1-13)	Inside heart: Infarct—posterior (1) Extension of infarct (15) Pericardial friction rub (3-10) Outside heart: Congestive heart failure—mild left (1-16) Shock, severe (16) Jaundice Hematemesis, mild (16) (cause not known)	Inside heart: Infarct—posterior walls of LV and RV, posterior portion of S Extension of infarct Pericarditis, fibrinous and adhesive Hemopericardium (no source found) Outside heart: Hydrothorax Congestion—lungs, liver, spleen, kidneys Atelectasis	Extension observed clinically following a rise in the prothrombin time for undilute blood from 22 to 24 to 32 secs on preceding days. The reading for the day of the extension was 30 secs
67 (A)	Male 63 years old Died 16th day Dicumarol (5-14)	Inside heart: Infarct—anterior (1) New secondary infarct—posterior (11) Outside heart	Inside heart: Infarct—posteroapical portion of LV Extension of infarct, hemorrhagic Scarring of healed infarcts (M) (BPI)—apical ⅓ of LV Outside heart: Congestion—lungs, abdominal viscera Atelectasis Infarct of spleen—recent Renal infarcts (M), old (BPI) Thrombosis of branch of right renal artery, old (BPI) Thrombosis of adrenal vein Cholecystitis	Patient died suddenly.
68 (No A)	Male 54 years old Died 17th day No anticoagulants	Inside heart: Infarct—anterior (1) Outside heart: Shock, moderate (3-17)	Inside heart: Infarct—anterior and lateral wall of LV Mural thrombus—anterolateral surface of LV Outside heart: Autopsy of chest only Hydrothorax Congestion—lungs Atelectasis	

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying During the Third Week (cont.)		
69 (A)	Female 53 years old Died 19th day Heparin (2-3) Dicumarol (2-18)	Inside heart Infarct—anteroseptal (1) Outside heart: Hematuria, mild (14) History of. Diabetes mellitus (for 19 yrs)	Inside heart Infarct—S Outside heart: Congestion—lungs, abdominal viscera Pulmonary edema	Patient found dead in bed Clinically considered death was possibly due to terminal arrhythmia
70 (A)	Female 72 years old Died 19th day Heparin (5-19)	Inside heart Infarct—anterior (1) Outside heart. History of. Diabetes mellitus (for 6 yrs) Diabetes osteomyelitis of foot (for 6 yrs) Diabetic gangrene, progressive	Inside heart Infarct, hemorrhagic—lower ½ of anterior wall of LV, anterior ½ of S Pericarditis, fibrinous Outside heart Pulmonary edema Congestion—lungs Bronchopneumonia, early—left Dry gangrene—1st and 2nd toes of left foot	Patient was a diabetic with gangrene of leg on admission to hospital During hospitalization coronary thrombosis developed The progression of gangrene made her condition desperate, and it was decided (a control case originally) to use heparin in an effort to control possible embolic phenomena, and still permit surgery if amputation became necessary Death was attributed clinically to either probable toxemia of gangrene or to terminal ventricular fibrillation.
71 (No A)	Male 70 years old Died 21st day No anticoagulants	Inside heart Infarct—anterior (1) Auricular fibrillation and ectopic ventricular beats (18-21) Outside heart· Congestive heart failure—mild to severe left, progressive (3-21) mild right (19-21) Pulmonary embolus (16) Pulmonary embolus, massive —left (21) History of. Hyperthyroidism with adenoma Exophthalmus	Inside heart Infarct—anterior wall of LV Mural thrombus—anterior wall of LV Fibrosis of healed infarct (BPI) —lateral surface of LV Aneurysmal dilatation—lateral wall of LV Outside heart Hydrothorax Congestion—lungs Pneumonia, lipoid Atelectasis Pulmonary emboli and infarcts (M), hemorrhagic—left and right lower lobes Hemothorax Aortic aneurysm—thoracic Mural thrombi—aorta Partial occlusion of left renal artery by thrombotic material from mural thrombus in abdominal aorta	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Third Week (cont.)		
65 (No A)	Male 67 years old Died 15th day No anticoagulants	Inside heart: Infarct—anterior (1) History of: Infarct—posterior (3 wks prior to onset) Outside heart: History of: *Diabetes mellitus*	Inside heart: *Infarct—S, anterior and apical* portions of LV Fatty infiltration of RV, marked Fibrosis of healed infarct (BPI)—posterior wall of LV Outside heart: Congestion-lungs, liver, spleen, kidneys *Pulmonary edema*	Patient first considered to suffer from gastrointestinal obstruction or cardiospasm because of continued anorexia and vomiting
66 (A)	Male 41 years old Died 16th day *Dicumarol (1-13)*	Inside heart: *Infarct—posterior (1)* *Extension of infarct (13)* Pericardial friction rub (3-10) Outside heart: Congestive heart failure—mild left (1-16) Shock, severe (16) Jaundice Hematemesis, mild (16) (cause not known)	Inside heart: *Infarct—posterior walls of LV* and RV, posterior portion of S *Extension of infarct* Pericarditis, fibrinous and adhesive Hemopericardium (no source found) Outside heart: Hydrothorax Congestion—lungs, liver, spleen, kidneys *Atelectasis*	Extension observed clinically *following a rise in* the prothrombin time for *undilute blood from* 22 to 24 to 32 secs. on *preceding days. The reading for the day of the* extension was 30 secs.
67 (A)	Male 63 years old Died 18th day Dicumarol (5-14)	Inside heart: *Infarct—anterior (1)* *New secondary infarct—posterior (11)* Outside heart	Inside heart Infarct—posteroapical portion of LV *Extension of infarct, hemorrhagic* Scarring of healed infarcts (M) (BPI)—apical ⅔ of LV Outside heart *Congestion—lungs, abdominal viscera* *Atelectasis* Infarct of spleen—recent Renal infarcts (M), old (BPI) *Thrombosis of branch of right renal artery, old (BPI)* Thrombosis of adrenal vein Cholecystitis	Patient died suddenly.
68 (No A)	Male 54 years old Died 17th day No anticoagulants	*Inside heart:* Infarct—anterior (1) Outside heart: Shock, moderate (3-17)	*Inside heart:* Infarct—anterior and lateral wall of LV Mural thrombus—anterolateral surface of LV Outside heart: *Autopsy of chest only* *Hydrothorax* Congestion—lungs Atelectasis	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Fourth Week (cont.)		
75 (A)	Male 63 years old Died 24th day Dicumarol (3-23)	Inside heart Infarct—posterior (1) Outside heart	Inside heart: Infarct, massive—posterior walls of LV and RV, posterior portion of S Interstitial hemorrhage in myocardium Mural thrombus, massive (50 gms.)—RV with propagation to right auricle and into base of pulmonary artery Fibrosis and scarring of healed infarct (BPI)—apex of LV, S Outside heart. Esophageal mucosal ulceration and hemorrhage	Patient died suddenly. The massive mural thrombus appeared to have developed during anticoagulant therapy. However, of the 21 days of anticoagulant therapy, the patient's prothrombin time was below 25 seconds on all but 2 days
76 (No A)	Female 57 years old Died 25th day No anticoagulants	Inside heart. Infarct—anterior (1) Pericardial friction rub (2) Outside heart History of. Diabetes mellitus	Inside heart. Infarct—S, posterior walls of LV and RV, anterior apex of LV Extension of infarct, hemorrhagic Mural thrombus—apex of LV Pericarditis, fibrinous Outside heart Congestion—lungs, liver, kidneys Renal infarcts, one recent—left kidney; multiple old (BPI)	Patient was convalescing uneventfully when he died suddenly
77 (No A)	Female 59 years old Died 25th day No anticoagulants	Inside heart: Infarct—anterior (1) History of Rheumatic heart disease with mitral stenosis Outside heart. Congestive heart failure—moderate left (1-25) History of. Gallbladder disease	Inside heart Infarct—anterior ¾ of S Extension of infarct, hemorrhagic Pericarditis, fibrinous Chronic rheumatic endocarditis of mitral and aortic valves Mitral stenosis and insufficiency *No* arteriosclerosis of coronaries Outside heart Hydrothorax Congestion—lungs, liver, spleen Renal infarct, old (BPI)—left kidney Cholelithiasis and cholecystitis	Clinically death was attributed to progressive heart failure
78 (A)	Male 47 years old Died 25th day Dicumarol (14-25)	Inside heart Infarct—posterolateral (1) Outside heart Congestive heart failure—severe left (4-25)	Inside heart Infarct, massive—posterior and lateral walls of LV and posterior portion of S Pericarditis Hemopericardium due to epicardial hemorrhage (900-1000 cc.) Outside heart *Autopsy of chest only*, except for small portion of liver Congestion—lungs, liver Ascites Bronchopneumonia	Recurrence of pain and increased congestive failure on day of death In a clinico-pathological conference on this case the conclusion was made that the recurrence of pain and increased failure on the day of death was due to cardiac tamponade from the excessive amount of bloody fluid in the pericardial sac

APPENDIX TABLE 91 (cont.)

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Fourth Week		
72 (*No A*)	Female *74 years old* Died 22nd day No anticoagulants	Inside heart: *Infarct—septal (1)* Outside heart Congestive heart failure—moderate right (9-?) Pulmonary embolus (3 and 11)	Inside heart· *Infarct—S, apex of LV and RV* Healed infarct (BPI)—S, apex of LV and RV Mural thrombi—LV; left and right auricular appendages Outside heart· Congestion—lungs, abdominal viscera Ascites Pneumonia, lobular Pulmonary emboli and infarcts (M)—all lobes Hemothorax (related to infarcts) *Portal cirrhosis of liver* Renal infarcts (M) Thrombosis of cystic vein	
73 (A)	Female 67 years old Died 24th day Heparin (13-15) Dicumarol (13-20)	Inside heart Infarct—posterior (1) New secondary infarct—diffuse (6) History of Infarct (20 months before onset; found by EKG this illness—posterior) Outside heart Congestive heart failure—mild left (11-24) Uremia—NPN 73 Phlebothrombosis—leg veins, bilateral	Inside heart Infarct—posterior wall of LV New secondary infarct—anterior wall of LV Scarring of healed infarcts (M) (BPI)—anterior wall of RV, posterior wall of RV Outside heart Hydrothorax Congestion—lungs, abdominal viscera Pulmonary edema Subcutaneous edema Atelectasis Leg veins not examined Cholelithiasis and cholecystitis	
74 (No A)	Female 70 years old Died 24th day No anticoagulants	Inside heart Infarct—posteroseptal and diffuse changes (1) Rupture of S (5) Outside heart· Congestive heart failure—mild left and right (5-7) Bronchopneumonia Pulmonary embolus (8) *Thrombosis of left* antecubital and left jugular veins (15-16)	Inside heart Infarct—posterior wall of LV and RV, posterior portion of S Rupture, septal—beneath the mitral region and leading to the apical region of the RV Mural thrombi—LV attached to S, recent, right auricular appendage, old (BPI) Pericarditis, fibrinous Outside heart Hydrothorax Subcutaneous edema—right leg only Atelectasis Bronchopneumonia—right Pulmonary thrombi (M)—large artery in lower right lobe Thrombosis of right popliteal, left subclavian, and left common iliac veins (veins clinically specified were not mentioned in the autopsy report as examined) Renal infarcts (M), old (BPI) Cholelithiasis	Patient hospitalized on 5th day and found to have loud systolic murmur which had not been heard at clinic shortly before admission *This* was diagnosed clinically as perforation of the septum

APPENDIX TABLE 91 (cont)

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, If Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstanc
		Cases Dying during the Fourth Week (cont.)		
82 (No A) (cont.)			Mural thrombi—LV, right auricular appendage	
		Outside heart Congestive heart failure—acute left (25-27) Uremia (26-27) Pneumonia	Outside heart Congestion—lungs, abdominal viscera Pulmonary edema Subcutaneous edema Pneumonia, lobular Mural thrombi—abdominal aorta Arteriolonephritis, accelerated, with necrotizing arteritis and severe focal nephrosis	
		Cases Dying during the Fifth Week		
83 (A)	Female 69 years old Died 29th day Dicumarol (3-28)	Inside heart Infarct—anteroseptal (1)	Inside heart Infarct—S and apex of the heart Extension of infarct Pericarditis	
		Outside heart Congestive heart failure—moderate left and right (20-29)	Outside heart Pulmonary edema Congestion—lungs, abdominal viscera	
84 (No A)	Male 47 years old Died 31st day No anticoagulants	Inside heart Infarct—posteroseptal (1)	Inside heart Infarct—posterior wall of LV near base, S Extension of infarct Rupture, incomplete—from myocardium into pericardial sac in area of aneurysmal dilatation in posterior basal portion of LV Hemopericardium	Patient gasped times while eatin and stopped br The heart bea rapidly and to for 2 or 3 minu stopped Thoug cally to have ventricular fib following recent occlusion
		Outside heart Shock, severe (31)	Outside heart Congestion—lungs, abdominal viscera Aspirated food and stomach contents plugging many of large bronchi	
85 (A)	Male 41 years old Died 34th day Dicumarol (2-29)	Inside heart Infarct—location could not be determined by EKG Extension of infarct—probably septal (34) History of *Two infarcts (4 and 6 yrs before onset)*	Inside heart Infarct—posterior wall of LV New secondary infarct—posterior portion of S Fibrosis and scarring of healed infarct (BPI)—anterior apex of LV	Patient sudden veloped respira tress and beca notic and pulse
		Outside heart History of Gout with renal disease (two mild attacks of gout during this illness) Hematuria, mild (attributed to renal disease secondary to	Outside heart Pulmonary edema Congestion—lungs, liver Gout tophi in kidney pelves with renal scarring Gouty arthritis	

Case No	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Fourth Week (cont.)		
78 (A) (cont.)		Pulmonary emboli, two or more (all occurring before hospitalization on the 12th day, and at least one of these occurred on the 10th day as evidenced by pain and hemoptysis)	Pulmonary infarcts (M)—lower left and right lobes	
79 (A)	Male 58 years old Died 25th day Dicumarol (2-22)	Inside heart Infarct—anterior (1) Extension of infarct (23) Pericardial friction rub (1-3) Outside heart Congestive heart failure—mild right (1-25) Shock, severe (23-25) Uremia and anuria (23-25)	Inside heart Infarct—anterior wall of LV with aneurysmal dilatation of apex of LV Extension of infarct, hemorrhagic Hemopericardium—hemorrhage from necrotic area Pericarditis, fibrinous Outside heart Hydrothorax Congestion—lungs, abdominal viscera Pulmonary edema Subcutaneous edema	Patient became comatose before death.
80 (A)	Male 58 years old Died 25th day Dicumarol (7-13)	Inside heart Infarct—posterior (1) Pericardial friction rub (17-25) Outside heart Staphylococcus septicaemia	Inside heart. Infarct—posterior walls of left and right ventricles, posterior portion of S Mural thrombus—posterior wall of RV Pericarditis, fibrinous Outside heart Leukoblastic hyperplasia of the bone marrow Congestion—lungs Bronchopneumonia with abscess formation Infarct of spleen, recent Miliary brain abscesses (M) Cholelithiasis and cholecystitis	
81 (A)	Male 49 years old Died 26th day Dicumarol (6-26)	Inside heart Infarct—anterior (1) New secondary infarct—location not specified (24) History of EKG taken at onset of this illness showed healed posterior infarct Outside heart	Inside heart. Infarct—anterior apical and mid-ventricular septum New secondary infarct—posterior walls of right auricle and posterior S Outside heart Congestion—lungs, abdominal viscera Ascites	
82 (No A)	Male 85 years of age Died 27th day No anticoagulants	Inside heart Infarct—anterior (1)	Inside heart· Infarct—LV (location not specifically reported but occlusion was in anterior descending branch of left coronary artery so probably the infarct was anterior); also right auricular appendage was probably involved	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Sixth Week (cont.)		
89 (No A)	Male 53 years old Died 41st day No anticoagulants	Inside heart Infarct—anteroseptal (1) Extension of infarct (33) Outside heart Agranulocytosis	Inside heart: Infarct—anterior wall of LV, anterior portion of S Extension of infarct, hemorrhagic Outside heart Pulmonary edema Congestion—lungs, abdominal viscera Hypoplasia of bone marrow, granulopoietic Pia arachnoidal hemorrhage (microscopic)	This patient developed agranulocytosis while being treated for a urinary obstruction and infection occurring on the 12th day. He was given sulphadiazine and sulphamerazine (0.5 gms. of each 4 times a day) On the 25th day the patient's blood count showed 2500 WBC, polys 89%, lymph 11%. On that day sulpha treatment was stopped and penicillin given. By the 40th day the patient's blood count was 2200 WBC, polys 0%, lymph 100%. On the 41st day he had a temperature of 103 6 and died suddenly. Clinically agranulocytosis was considered an important, if not the chief, cause of death.
		Cases for Whom Diagnosis of Myocardial Infarction was Not Confirmed at Autopsy		
90 (A)	Female 61 years old Died 6th day Dicumarol (5)	Inside heart Infarct—anterior (1) Auricular fibrillation, numerous attacks (3-6) History of. Infarct—anterior (year before onset) Outside heart Congestive heart failure—moderate left (3-6), mild right (5-6)	Inside heart No infarct of recent origin found Arteriosclerosis of coronary arteries, moderate Fibrosis of healed infarct (BPI)—anterior wall of LV, anterior portion of S Outside heart Congestion—spleen Atelectasis	Just prior to death patient was found pale, sweating, and breathing rapidly. Her heart sounds were very faint. No explanation for death is apparent from the autopsy report and therefore may be attributed to terminal cardiac arrhythmia as suggested in clinical diagnosis
91 (A)	Male 61 years old Died 16th day Heparin (7-8) Dicumarol (7-14)	Inside heart· Infarct—septal (1) Outside heart Bronchopneumonia, confluent	Inside heart. No infarct of recent origin found Arteriosclerosis of coronary arteries, severe Scarring of healed infarct (BPI)—posterior and basal, lateral to the S (chambers involved not specified) and S Pericarditis, chronic Outside heart Bronchopneumonia Congestion—lungs, abdominal viscera Thrombosis of adrenal vein	Clinically death was attributed to confluent bronchopneumonia which had failed to respond to penicillin In the light of autopsy findings, it was considered clinically that the changes noted in the ECG reading might be attributed to coronary insufficiency.

APPENDIX TABLE 91 (cont.)

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
		Cases Dying during the Sixth Week		
86 (A)	Male 60 years old Died 37th day Dicumarol (33-36)	Inside heart: Infarct—anterior (1)	Inside heart: Infarct—lower half of entire circumference of LV including S Extension of infarct Mural thrombus—LV Pericarditis, fibrinous	
		Outside heart Congestive heart failure—mild left and moderate right (8-37) Pulmonary embolus—right lower lobe (1) Pulmonary embolus and phlebothrombosis in right calf (32) Massive pulmonary embolus terminally Cholecystitis and cholelithiasis, subacute Diabetes mellitus, mild	Outside heart: Hydrothorax Congestion—lungs, abdominal viscera Leg veins not examined Cholecystitis and cholelithiasis Renal infarct, recent	
87 (No A)	Male 72 years old Died 39th day No anticoagulants	Inside heart: Infarct—anterior (1)	Inside heart. Infarct—S, LV (details of location were not reported) Mural thrombus—apex of LV Pericarditis, fibrinous and adhesive Aneurysmal dilatation—apex of LV	
		Outside heart History of. Cerebrovascular accident with residual hemiparesis and aphonia (4 yrs before onset)	Outside heart: Congestion—liver Bronchopneumonia—right Pulmonary embolus—inferior branch of right pulmonary artery Pulmonary infarcts (2)—lower left and lower right lobes Focal hemorrhage and atrophy in cerebral cortex Encephalomalacia	
88 (A)	Male 70 years old Died 39th day Dicumarol (3-35)	Inside heart. Infarct—anterior and diffuse changes (1) Extension of infarct (31)	Inside heart: Infarct—anterior wall of LV, anterior portion of S Extension of infarct, hemorrhagic Pericarditis, fibrinous	
		Outside heart Congestive heart failure—mild left (36-39)	Outside heart Hydrothorax Congestion—lungs, abdominal viscera	

Case No.	Type of Case	Clinical Diagnoses (Days of illness condition was present, when reported, given in parentheses)	Corresponding Autopsy Findings, if Any, and Other Selected Major Findings, Particularly Cardiovascular	Special Circumstances
Cases Dying during the Sixth Week (cont.)				
89 (No A)	Male 53 years old Died 41st day No anticoagulants	Inside heart. Infarct—anteroseptal (1) Extension of infarct (33) Outside heart Agranulocytosis	Inside heart: Infarct—anterior wall of LV, anterior portion of S Extension of infarct, hemorrhagic Outside heart: Pulmonary edema Congestion—lungs, abdominal viscera Hypoplasia of bone marrow, granulopoietic Pia arachnoidal hemorrhage (microscopic)	This patient developed agranulocytosis while being treated for a urinary obstruction and infection occurring on the 12th day. He was given sulphadiazine and sulphamerazine (0.5 gms. of each 4 times a day) On the 35th day the patient's blood count showed 2300 WBC, polys 89%, lymph 11%. On that day sulpha treatment was stopped and penicillin given. By the 40th day the patient's blood count was 2200 WBC, polys 0%, lymph 100%. On the 41st day he had a temperature of 103 6 and died suddenly. Clinically agranulocytosis was considered an important, if not the chief, cause of death.
Cases for Whom Diagnosis of Myocardial Infarction was Not Confirmed at Autopsy				
90 (A)	Female 61 years old Died 6th day Dicumarol (5)	Inside heart Infarct—anterior (1) Auricular fibrillation, numerous attacks (3-6) History of Infarct—anterior (year before onset) Outside heart Congestive heart failure—moderate left (3-6), mild right (5-6)	Inside heart No infarct of recent origin found Arteriosclerosis of coronary arteries, moderate Fibrosis of healed infarct (BPI)—anterior wall of LV, anterior portion of S Outside heart Congestion—spleen Atelectasis	Just prior to death patient was found pale, sweating, and breathing rapidly. Her heart sounds were very faint. No explanation for death is apparent from the autopsy report and therefore may be attributed to terminal cardiac arrhythmia as suggested in clinical diagnosis
91 (A)	Male 61 years old Died 18th day Heparin (7-8) Dicumarol (7-14)	Inside heart Infarct—septal (1) Outside heart Bronchopneumonia, confluent	Inside heart No infarct of recent origin found Arteriosclerosis of coronary arteries, severe Scarring of healed infarct (BPI)—posterior and basal, lateral to the S (chambers involved not specified) and S Pericarditis, chronic Outside heart Bronchopneumonia Congestion—lungs, abdominal viscera Thrombosis of adrenal vein	Clinically death was attributed to confluent bronchopneumonia which had failed to respond to penicillin. In the light of autopsy findings, it was considered clinically that the changes noted in the ECG reading might be attributed to coronary insufficiency.

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